Survival of Patients with Ischemic Heart Disease
After Attenuation of Central Autonomic Nervous System Dysfunction,
Monitored by Sensitivity of Sternum Periost to Painful Pressure

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Abstract

Background: Autonomic nervous system dysfunction (ANSD) is known to be associated with multiple conditions, including stress, insomnia, allergies, and ischemic heart disease (IHD). Treatment by pharmaceutical or surgical means addresses symptoms but may have no effect on the ANSD. Central ANSD is reflected in values of the pressure-pain sensitivity (PPS) at the sternum.

Objectives: We tested if cerebral regulation of ANSD in terms of non-pharmacological attenuation of the PPS measures was associated with lower the all-cause mortality of patients with IHD.

Results: During median follow-up of five years, the number of deaths among the patients of the adjunct Intervention was significantly lower than among the patients undergoing Control treatment (P=0.017). The all-cause mortality of the Intervention group was also lower than that of the general Danish population, matched for gender, age and observation period (P = 0.010).

Conclusion: The Intervention designed to attenuate central ANSD by lowering measures of PPS reduced the all-cause mortality of patients with IHD during a period of five years after the three-month Intervention period.

Introduction

We tested the association of the Intervention into elevated PPS measures with the subsequent all-cause mortality. We completed two analyses of survival in a prospective follow-up study to the RCT reports published by Bergmann et al. (2014) and Ballegaard et al. (2015). First, we compared the 5-year mortality of Intervention and Control groups by Poisson regression. Second, we compared the five-year mortality of the two RCT groups with the 5-year mortality of normal Danish populations of individuals of the same age and sex as the patients of the RCT groups.

We tested the association knowing that the autonomic nervous system (ANS) regulates functions of the human body by adjusting the balance between the sympathetic and parasympathetic nervous systems. The dynamic processes of adaptation in the face of adversity are orchestrated by a dynamic readjustment of the two systems known as resilience (McEwen, 2016; Carnevali et al., 2018). Autonomic nervous system dysfunction (ANSD) is defined as a reduction of this resilience, associated with morphological and functional changes of brain regions, e.g., hippocampus, amygdala, and prefrontal cortex (McEwen et al., 2016). ANSD may appear as parasympathetic hypoactivity or sympathetic hyperactivity or predominance (Spallone, 2019).

ANSD is diagnosed by a combination of results of a range of tests, including Table Tilting (Novak, 2011) and Heart Rate Variability (Spallone, 2019) tests, both addressing the autonomic functions of the cardiovascular system. Recently, we claimed sensitivity to painful pressure of the chest bone periosteum (PPS) to be a potentially useful measure of central autonomic sympathetic function, with elevated PPS measures indicating central ANSD (Faber et al 2021), linking link persistent stress, depression, and IHD (Grippo and Johnson, 2009; Steptoe and Kivimäki, 2012; Staufenbiel et al., 2013; Wentworth et al., 2013), independently of other conventional risk factors (Thayer and Lane, 2007).

There is no evidence-based treatment of ANSD, but peripheral nerve stimulation has been suggested as a method of reduction of sympathetic nervous system hyperactivity (Güemes and Georgiou, 2018). Here, we tested the effect of this treatment of ANSD on the survival of patients with IHD. The treatment (the "Intervention") consisted of a non-pharmacological program of (1) daily repeated PPS measurements meant to induce cognitive reflection on the perceived level of stress, in order to enhance compliance as well as to monitor the long-term effect, (2) daily peripheral non-noxious sensory nerve stimulations of a specific dermatome associated with the PPS site at the sternum for repeated autonomic reflex elevation of the noxious withdrawal reflex threshold for PPS reduction and hypothetical ANSD reversal, (3) selection of free-choice physical and mental exercises, and (4) ongoing professional evaluation of the PPS measurements with proactive supervision in cases of missing or deviating measurements (Bergmann et al., 2014).

We tested the null hypothesis that this three-month Intervention would have no effect on the all-cause mortality of patients with IHD and elevated PPS measure during the subsequent five years. We tested the null hypothesis by comparing the five-year mortality of the members of the two groups of the initial RCT (Bergmann et al., 2014), and by comparing the five-year mortality of each of the two RCT groups with subgroups of the general Danish population in the same years, matched for age and gender of the members of the two RCT groups.

Materials and Methods

Objective, design, participants, and setting

We tested the null hypothesis that reduction of elevated PPS measures during a three-month program of non-pharmacological Intervention would not reduce the five-year mortality of patients with chronic but stable IHD. The test was designed as a follow-up to the previously reported three-month randomized controlled trial (RCT) of 213 patients (Bergmann et al., 2014; Ballegaard et al. 2015). The choice of five years of observation made use of five-year intervals of data from Statistics Denmark of the general Danish population, matched for gender, age, and observation period. We compared the five-year all-cause survival of the patients of the Intervention group to the all-cause survival of the group of Control subjects, and we separately compared both of these groups to matching versions culled from the data of the general Danish population, matched for age, gender, and observation period. The cohorts of the original RCT trial consisted of 106 actively treated patients (i.e., subjects receiving the Intervention designed to reduce elevated PPS measures), and 107 Control subjects (Figure 1). Mean age at inclusion was 62.7 (±8.1 SD) years, with 73% males and 27% females. The calendar years of inclusion into the study were 2011/2012 for 80/26 patients of the Intervention group, and 79/28 of the Control group, respectively. No contact was made between subjects and research team after the three months of RCT.

Outcome measure

Healthcare data for Denmark is available for anonymized research via Statistics Denmark and the Central Population Register provides information on vital status and all-cause mortality in Denmark. The outcome measure was all-cause mortality, as obtained from this register. Due to General Data Protection Regulations of Statistics Denmark, any number of clinical events less than or equal to three used in statistical analysis must be presented as “three or fewer events”. The present study complies with this regulation.

Intervention and Control groups

Results of the previous three-month Intervention were reported in detail (Bergmann et al., 2014; Ballegaard et al., 2015). Members of the RCT Intervention group completed the three-month non-pharmacological, self-care stress reduction program, including home use of a PPS measuring device, with instruction to perform daily home PPS measurements and sensory nerve stimulations designed to reduce the PPS measurements. During the three months, professional backup was conducted by ongoing on-line monitoring of the PPS measures, with provision for a professional instructor to act proactively in case of missing or deviating measures. Patients of the RCT Control group received the information that the level of persistent stress was elevated and unfavourable for the disease prospects, as well as a book written by an acknowledged medical stress specialist that underscored the association and gave advice for general stress management. The programs of the two groups included no medication other than the prescriptions active at the beginning of the study, and the medications remained unchanged during the last one month prior to onset of, as well as during, the three-month study periods. At the end of the three-month study period, patients of the RCT Intervention group were encouraged to continue the daily efforts with the goal of maintaining low PPS, but degree of compliance, if any, was not registered.

Statistics

Via the unique 10-digit central person registry (CPR) number, all persons in Denmark can be tracked with respect to mortality. We conducted three all-cause mortality analyses (for statistical details, see

supplementary material). One analysis compared the all-cause mortalities of the Intervention and Control groups of subjects of the RCT on an intention-to-treat basis. We used Poisson regression of rare outcome events with SAS Statistical Software package version 9.4 (SAS Institute Inc., Gary, NC, USA) and Stata Software version 15 (StataCorp, College Station, TX, USA). The additional analyses compared the all-cause mortality of each of the two groups of the RCT with subsets of the general Danish population, matched for age, gender, and observation period. Statistics Denmark delivers all-cause mortality data for five-year intervals, allowing us to compare each of the 213 patients of the RCT to approximately 35.000 Danes with the same age and gender for the five-year observation period, each starting at the time of the entry into the original RCT study (Bergmann et al 2014).

We predicted the distribution of deaths in subgroups of persons from the Danish general population, based on data from Statistics Denmark with the same age and gender profiles of each individual patient of the RCT (Bergmann et al 2014). While a one-sided t-test is consistent with the null hypothesis that mortality would not decline in the Intervention group, we present results of both one-sided and two-sided t-tests (Cox et al., 1977).

The distribution of the individual five-year risk of death of the 106 persons of the RCT Intervention group and the 107 subjects of the RCT Control group is non-symmetrical (Figure 1). Based on the background population of Denmark, we estimated the distribution of the number of deaths in a group similar to the Intervention and in a group similar to the Control group, considering the individual risks. The two groups were similar with respect to the predicted number of deaths of 7.97% and 8.34% for the Intervention and Control groups, respectively (Figures 2 and 3).

Results

Intervention versus Control groups

During the years 2011-2016, we observed 11 or fewer deaths during the median period of observation of 5.2 years, including three or fewer subjects from the Intervention group, and eight subjects from the Control group. At baseline, 20 patients of the Intervention group and eight patients of the Control group had Type 2 Diabetes Mellitus (between group P=0.027). Adjusting for this difference, Poisson regression of survival data from the participants of the RCT trial disclosed a significant difference of survival between the subjects of the Intervention and Control groups (one sided t-test, P=0.017; two-sided t-test, P = 0.035). All-cause mortality was lower for the Intervention group with incidence rates (IR) of 3.7 per 1000 person-years, and adjusted incidence rate ratios (IRRs) of 0.19 (95% confidence interval: 0.04–0.93), compared with Control subjects (IR 14.8 per 1000 person-years)

As shown in Figure 4, a mean prediction of 1.81896 deaths derived from the Intervention mean of 3.33 deaths per 1000 person-years (py), obtained by applying 3.33 per 1000 py to the experiment of 106 x 5.2 py where 106 is the number of subjects and 5.2 the number of years followed, i.e., 3.3 x (106 x 5.2/1000) = 1.81896. The period of 5.2 years is the median, as half of the subjects were followed for less than 5.2 years, and half were followed for more than 5.2 years. The prediction of 1.81896 years is therefore the Poisson mean that applies when all 106 participants were followed for exactly 5.2 years. Similarly for the Control group, the theoretical mean prediction of 8.23472 deaths derived from the Control group mean of 14.8 deaths per 1000 person-years (py), obtained by applying the 14.8 per 1000

py to an experiment of 107 x 5.2 py where 107 is the number of subjects and 5.2 the number of years followed, i.e., 14.8 x (107 x 5.2/1000) = 8.23472.

Intervention and Control groups versus General Population of Denmark
Table 1 shows the risks of death, the expected number of deaths as well as the observed number of deaths, within the five-year observation period of members of the Intervention and Control groups of the RCT, matched to subjects from the general Danish population with the same age and gender, according to Statistics Denmark. When compared to the expected number of deaths during the five-year observation period, the number of three or fewer deaths of the Intervention group was significantly lower than the expected number of eight deaths (one-sided t-test, P=0.010; two-sided t-test, P=0.043, while the observation of eight deaths in the Control group matched the prediction (P = 0.54).

Discussion

Main findings

The present RCT tested survival after a specific hypothetical adjunct Intervention into ANSD in IHD, claimed to ameliorate an assumed dysfunctional cerebral regulation of autonomic function, expressed as pathologically elevated measures of PPS. We conducted the original RCT as a single-center, two-armed, parallel-group, observer-blinded, randomized (1:1), clinical superiority trial, and subsequently tested the effect of the non-pharmacological intervention in terms of the subsequent five-year all-cause mortality. The Intervention was designed to lower the elevated PPS reading at the periosteum of the sternum as a measure of ANSD. The findings rejected the null hypothesis that three months of PPS-guided non-pharmacological adjunct Intervention would not lower the five-year all-cause mortality of patients with IHD and elevated PPS measures above 60 arbitrary units at baseline.

In previous RCT of IHD patients, the Intervention lowered the questionnaire ratings of depression reported by the patients (Bergmann et al., 2014), and lower depression ratings are known to be associated with lower incidence of all-cause mortality in IHD patients (Lichtman et al 2014) that in turn has been linked to lower ANSD ratings (Grippo and Johnson, 2009). The Intervention also improved measures of systolic blood pressure response to tilt-table testing (Ballegaard et al., 2015), also known to be associated with lower levels of ANSD. Both effects were reduced in the presence of beta-adrenergic medication (Ballegaard et al., 2016), consistent with the hypothesis advanced by Bergmann et al. (2014) and Ballegaard et al. (2015) that reduction of the degree of ANSD, measured as a reduction of an elevated PPS, is due to lower autonomic sympathetic activity, a notion which is further supported by the association between PPS and sympathetic cardiovascular neuropathy in persons with type 2 diabetes (Faber et al 2021).

Second, we compared the five-year all-cause mortalities of the two RCT groups to subsections of the general Danish population, matched for gender, age, and observation periods. The findings rejected the null hypothesis that three months of adjunct Intervention would not lower the five-year all-cause mortality when compared to the general Danish population matched for gender, age and observation period. However, the findings did not reject the null hypothesis that the five-year all-cause mortality of the RCT Control group would equal that of the general Danish population, matched for gender, age, and observation period.

Thus, the present findings are not consistent with the null hypothesis that three months of PPS-guided non-pharmacological adjunct Intervention would not lower the five-year all-cause mortality of IHD patients with elevated PPS. The subsequent evaluation of possible other causes of the effect of the Intervention revealed no significant effect other than the lowering of elevated PPS values, interpreted as indicative of attenuation of central ANSD.

As the inclusion criterion of participation was ANSD at baseline, defined as an elevated PPS measure of at least 60 units, the findings underscore the association between ANSD indicative of increased sympathetic autonomic brain activity measured by PPS, and the prognostic association with all-cause mortality. The decreased mortality of the Intervention group compared to the general population underscores the association between PPS measures and central autonomic function.

Modulation of sensitivity to painful pressure

The afferent leg of the neurophysiological pain loop can be modulated by non-pharmacological sensory nerve stimulation in patients with painful diabetic neuropathy (Tesfaye et al., 2010), as well as by activity of efferent pathways from cerebral neurotransmission, and by receptor blockade in the spinal cord (Richner et al., 2019). The reduction of the PPS measure achieved by the present Intervention appears to be mediated by a central reflex loop (Faber et al 2021). Furthermore, non-painful cutaneous sensory nerve stimulation releases the hypothalamic peptide oxytocin that reduces pain and stress measures, restores autonomic function, and engages beta-adrenergic receptors (Uvnäs-Moberg et al., 2014). The evidence suggests an association of the PPS measure to the orexin receptor system of the lateral hypothalamus rather than the oxytocin system (Faber et al 2021).

PPS measure, ANSD, and mortality in patients with ischemic heart disease

It is well established that ANSD is associated with increased mortality in IHD (Thayer et al., 2007). The association between PPS and central ANSD has been established by a series of studies, including tilt table response in IHD (Ballegaard et al., 2015, 2016) and cardiovascular neuropathy in diabetes patients (Faber et al., 2021). Despite substantial improvements of the survival of patients with ischemic heart disease, the patients still face an elevated risk compared to the general population (Sidney et al., 2018), especially if the patients have type 2 diabetes mellitus (Quinones et al., 2015). Given that all patients of the original RCT had ischemic heart disease, and that a substantial number had diabetes as well, it is of considerable interest that we found the mortality of the Intervention group to be significantly lower than that of the general Danish population.

We cannot rule out that a measure of biofeedback, other than the PPS measures, would similarly be indicative of an effect on all-cause mortality. However, in the available literature of RCT of IHD, we found no evidence of reduction of any individual cardiovascular risk factor that lowered all-cause mortality to a level that surpassed that of the general population, matched for gender, age and observation period (Sidney et al., 2018).The lack of such evidence supports the claim that reduction of central ANSD is achieved by the Intervention, as monitored by the reduction of the elevated PPS. We interpret the PPS reading as a measure of function of the ANS that originates at levels of the ANS hierarchy higher than those of other individual risk factors associated with IHD (Faber et al., 2021).

To be sure, in a series of RCT, reduction of elevated PPS measures was found to be associated with reduction of a broad range of independent health risk factors that are known to affect mortality, including autonomic dysfunction measured as the tilt table test response (Ballegaard et al., 2015), as well as blood pressure, heart rate, work of the heart measured as the Pressure-Rate Product (i.e., systolic blood pressure x heart rate), serum lipids, glycated hemoglobin A1c, body mass index, low-grade inflammation (Ballegaard et al., 2014), depression, stress and general health measured by questionnaires (Bergmann et al., 2014). We note that the health risk factors of this list are all affected by changes of the autonomic nervous system as recorded by PPS measures (Ballegaard et al., 2014, 2015), and autonomic nervous system dysfunction has been linked to effects of these factors, including impaired pain control (Chalaye et al., 2012), cardiovascular disease, depression, persistent stress (Grippo and Johnson, 2009; Steptoe and Kivimäki, 2012), metabolic syndrome, i.e., hypertension, disturbed lipid and glucose metabolic rates with disturbed body fat distribution (Rosmond, 2005), and low-grade inflammation (Bhati et al., 2019). Taking these findings into account, the present evidence does not reject the claim that the PPS measure reflects a central ANS function that affects the risk factors (Faber et al., 2021).

Can confounding factors that may affect IHD mortality explain the present results? The null hypothesis was based on the following potentially confounding factors, all of which have been evaluated for possible effect on all-cause mortality in IHD patients, with a negative result. Physical exercise rehabilitation has been found to reduce cardiovascular mortality, but not all-cause mortality, implying that death from other causes may occur earlier (Anderson et al., 2016). Both reduction and gain of weight have been found to increase all-cause mortality (Dong et al., 2018). Yoga-based cardiac rehabilitation programs do not affect the rate of cardiac events or all-cause mortality (Prabhakaran et al., 2020). A recent Cochrane review (Richards et al., 2018) evaluated the effect of psychological intervention, relaxation therapy, cognitive behavior therapy, mindfulness, transcendental meditation, health education, stress management and life style programming, tele-health intervention, and psychotherapy and revealed no effect on all-cause mortality.

Furthermore, cognitive therapy towards low perceived social support has been found not to lower all-cause survival, or the rate of a new cardiac event (Schneiderman et al., 2004), and although self-reported measures of religiosity and spirituality have been reported to affect all-cause mortality in healthy persons, no studies evaluated these activities as forms of secondary intervention in IHD (Koenig, 2012). With respect to diets, including Mediterranean diet, the authors of a recent Cochrane review concluded that there is a paucity of evidence for effects of secondary intervention into IHD (Rees et al., 2019). In other Cochrane reviews, the authors examined the effect of dietary reduction of saturated fat or Omega 3 fatty acids and found no significant effect on all-cause or cardiovascular mortality (Abdelhamid et al., 2018; Hooper et al., 2020). Thus, none of the potential confounders that patients may have experienced during the five-year observation period have been found to reduce the all-cause mortality of IHD patients to a level that surpasses that of the general population, matched for gender, age, and observation period or to reduce all-cause mortality in IHD. Other possible explanations of the reduction of all-cause mortality have not been identified, leaving the reduction of central ANSD as the most plausible explanation of the lowered mortality.

Strengths and limitations

Access to mortality data is a well-documented and validated application of information from Statistics Denmark. We do not know what the patients did after the Intervention, but we interpret the rejection of the null hypothesis to mean that ANSD was reversed by the Intervention that included repeated autonomic reflex activation and personal empowerment, and that normal ANS function would be maintained unless or until a new and severe strain would cause a recurrence of ANSD. Furthermore, we also interpret the findings to suggest that the subjects of the Intervention continued measuring the PPS at the end of the three months of RCT (Bergmann et al., 2014), for continued personal reflection on the level of stress, and treatment of self by sensory nerve stimulation to maintain non-elevated PPS values by subjects aware of the possible benefit. However, we collected the results of mortality during the subsequent five years from nationwide registers, with no further contact between patient and research team, in order to observe the natural course after the Intervention and to exclude potential influence from researcher bias.

It is a challenge to the statistics that we observed only a small number of deaths. We expected the statistical tests of the effect to have low power and to reflect a high risk of Type II errors. For this reason, we tested the effect of Intervention on mortality in three ways. We chose the Poisson regression because of the small number of events and we compared the mortalities of the participants of the Intervention and Control groups and those of the subgroups of the general population. Regardless of the expected low power of the statistical tests, the results of the three analyses were consistent with the rejection of the null hypothesis. Furthermore, the combination of a statistically significant reduction in mortality and the expected low power of the statistical tests increased the strength of the evidence supporting the conclusions, as small and inconsequential differences in mortality would not have resulted in significant test results. We find that the five-year risk of death of the RCT Control group corresponds to the five-year risk of death in the matched normal population, although a slightly increased risk was to be expected as all the participants had chronic ischemic heart disease and some in addition type-2 diabetes (Quinones et al., 2015; Sidney et al., 2018). However, the normal risk may be explained by the RCT Control group's active interaction with the researchers that could have affected both the level of stress (Bergmann et al., 2014) and the level of autonomic dysfunction in a beneficial way (Ballegaard et al., 2015).

It may be considered a limitation that the study group consisted of close to 200 patients only. By comparison, an RCT evaluating the cardiovascular risk in response to a pharmaceutical treatment of patients with type 2 diabetes included 9.000 patients. In that study, comparison of the all-cause mortality of the active group with that of the control group, 95% confidence limits were 0.03 – 0.26 (Marso et al., 2016). In the present study, the corresponding 95% confidence limits were 0.04 – 0.93. As such, the incidence rate ratios were 0.85 in the study of Marso et al and 0.19 in the present study, a 4.5 times greater incidence rate ratio in the present study of 200 patients indicative of a significant between-group difference.

Other weaknesses may be the clinical relevance of the results and the actual number of deaths due to the General Data Projection Regulations of Statistics Denmark. Tests of hypotheses involve more than checks of whether a P-value is lower than 5%. When the research hypothesis is a historical null-hypothesis, the magnitude of the P-value is a measure of how strongly the statistical test rejects the hypothesis, with lower P-values providing stronger rejection. In this case, the null hypothesis claimed

that the intervention would fail to reduce all-cause mortality. The rejection is supported by clinical experience and relevant risk factor reductions (Ballegaard et al., 2014, 2015; Bergmann et al., 2014), as well as on two other prospective observational studies, in which it was specifically concluded that the results (i.e., reduced overall mortality observed of an non-pharmacological PPS-reducing intervention when compared to that of the general Danish population matched for gender, age, and observation period) would only be valid if tested by a strict RCT design (Bergmann et al., 2014, Ballegaard et al., 2015). In this respect, the present conclusions are consistent with the significance from one-sided t-tests, and the restricted presentation of the number of deaths does not affect the significance or the confidence intervals. However, the rejection was also significant when tested by two-sided statistics. Finally, large sample sizes are preferable also for evaluation of potential side effects. However, this is of less concern here because previous studies showed that the present intervention carried neither risks nor side effects (Bergmann et al., 2014; Ballegaard et al., 2015).

Conclusions and possible clinical applications and perspectives

The present results of reduced mortality after the Intervention add to previous reports of evidence of benefits. They also imply that the proposed Intervention into autonomic dysfunction and ischemic heart disease potentially is applicable as a supplement to conventional treatment of ischemic heart disease. Central autonomic dysfunction is a key to the understanding of cardiovascular pathology and thus to IHD that may not be fully addressed by present pharmaceutical and surgical means. The PPS tool and the associated treatment are applicable to assessment of central autonomic dysfunction in patients with IHD for therapeutic and preventive purposes, and with no risk of side effects. Autonomic dysfunction is also important to many common human complaints, common diseases, and even life-threatening health conditions, at present treatable only by pharmaceutical or surgical means that do not address the autonomic dysfunctional aspects of the condition.

Symbols, abbreviations and acronyms

ANS – autonomic nervous system
ANSD – autonomic nervous system dysfunction
PPS – Pressure pain sensitivity
IHD – ischemic heart disease
IR - Incidence rate
IRR - Incidence rate ratio

Conflicts of interest

Søren Ballegaard is a shareholder in the company UllCare A/S that holds the patent for the PPS-measurement device. He did not participate in patient selection, examinations or evaluation of the examinations. No other author was associated with UllCare A/S or has any economic benefit from the study.

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Author contributions

JF made major contributions to all aspects of the study and the writing of the manuscript. AG made major contributions to the presentation and interpretation of the results and preparation of the manuscript. SB is the inventor of the Device and designer of the adjunct Intervention applied to the patients of the Intervention group, and revision of the manuscript. BK, CS, and SK made contributions to the statistical analysis, interpretation of results, and preparation of the manuscript. EE and FG contributed to the interpretation of the results and preparation of the manuscript. All authors approved the submitted version.

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Tables and Figures

Table 1. Distribution of five-year risks of death (range and mean), predicted number of deaths in the Intervention and Control group of the RCT when matched to general Danish populations for age, gender and observation period, and observed number of deaths (C.I = confidence limits ; N.S: = non significant) (for statistical details: see Supplementary material)

RCT group	n	Range (mean)	Predicted number of deaths	Number of deaths (95 % C.I)	P- value
Intervention group	106	0.0043 - 0.2123 (0.075)	7.97	≤ 3 (0.5-6.6)	0.01
Control group	107	0.0076 - 0.2123 (0.078)	8.33	8 (3.8-14.1)	N.S.

Legends

Figure 1: Distributions of individual 5-year risks of death for the subjects of the RCT Intervention (N = 106) and Control (N =107) groups. Each column represents one subject.

Figure 2: The accumulated number of expected 5-year deaths for the RCT Intervention and Control groups, respectively (Y-axis). The abscissa is the magnitude of the 5-year accumulated risks for the individual subjects, shown as groups of subjects within fractions of 0.05 % risk of death within the 5-year observation period matched to the general Danish population with respect to gender, age, and observation period.

Figure 3: Distribution of probabilities of number of deaths during the 5-year observation period in two groups similar to the RCT Intervention and Control groups, respectively, when they are matched to the general Danish population for gender, age and observation period.

Figure 4: The theoretical prediction distribution of number of deaths in the RCT Intervention group based on an incidence rate of 3.3 per 1000 person-years, and the RCT Control group based on the incidence rate of 14.8 per 1000 person-years.

Figure 1. RCT Populations

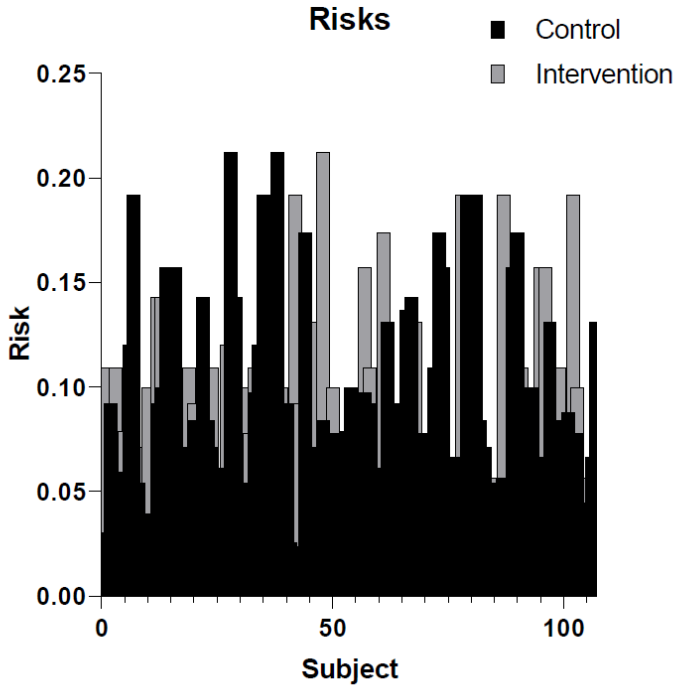

Figure 2. Predicted deaths from background population of Denmark

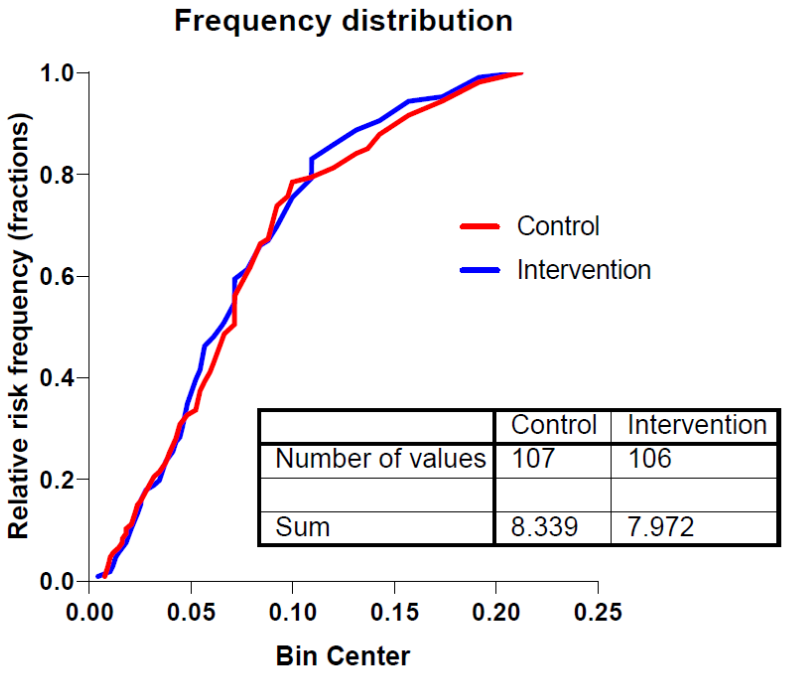

Figure 3. Predicted distribution of deaths in RCT Populations

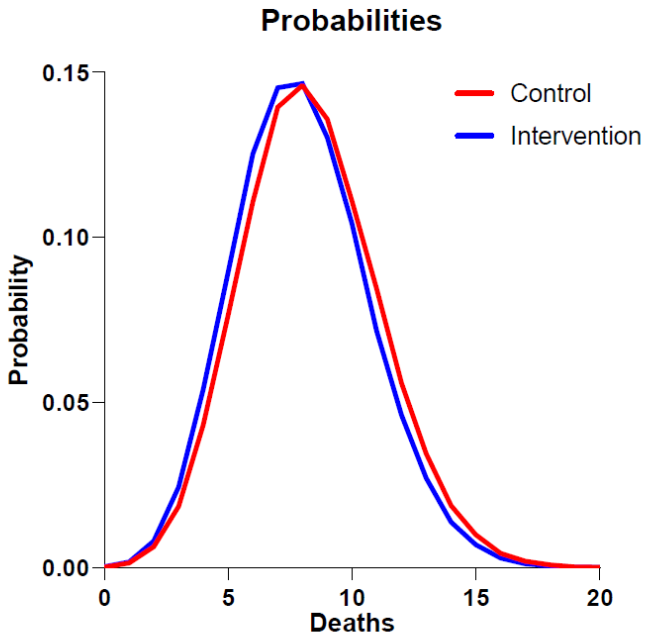

Figure 4. Distribution of probable deaths in RCT Populations