Design of a dietary intervention study in colorectal cancer patients

-Evaluation of dietary and physical activity assessment methods in colorectal cancer patients

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Oslo, February 2018

Hege Berg Henriksen

List of papers

Paper I

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Paper II

Hege Berg Henriksen, Monica Hauger Carlsen, Ingvild Paur, Sveinung Berntsen, Siv Kjølsrud Bøhn, Anne Juul Skjetne, Ane Sørlie Kværner, Christine Henriksen, Lene Frost Andersen, Sigbjørn Smeland, Rune Blomhoff (2017). Relative validity of a short food frequency questionnaire assessing adherence to the Norwegian dietary guidelines among colorectal cancer patients. *In press, Food & Nutrition Research 2018,62:1306 - http://dx.doi.org10.3402/fnr.62.1306*

Paper III

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Abbreviations

AICR	American Institute of Cancer Research
BMI	Body mass index
CRC	Colorectal cancer
CRC-NORDIET study	The Norwegian dietary guidelines and colorectal cancer survival study
CUP	Continuous Update Project
CVD	Cardiovascular disease
DFS	Disease-free survival
DNA	Deoxyribonucleic acid
EPIC	European Prospective Investigation into Cancer and Nutrition study
FFQ	Food frequency questionnaire
FBDG	Food-based dietary guidelines
FRESH START study	A Sequentially Tailored, Diet and Exercise Mailed Print Intervention Among Breast and Prostate Cancer Survivors
GLOBOCAN	Global Burden of Cancer Study
HR	Hazard ratio
HUNT-PAQ	The Nord-Trøndelag Health Study physical activity questionnaire
IARC	International Agency for Cancer Research
ICD	International classification of diseases
IPAQ-sf	Short form International physical activity Questionnaire
KBS	Kost Beregnings System (The food composition database and nutrient calculation system)
METs	Metabolic equivalents
MI	Motivational interview
MPA	Moderate physical activity
MVPA	Moderate-to- vigorous physical activity
NOWAC	The Norwegian Women and Cancer Study
NORKOST	Norwegian nationwide survey
OS	Overall survival
PA	Physical activity
RCT	Randomised controlled trial
RENEW	Reach Out to Enhance Wellness trial
SOP	Standard operating procedures
SWA	SenseWear Armband Mini
TNM	Tumor Node Metastases
VPA	Vigorous physical activity
WCRF	World Cancer Research Fund
WHEL	The Women`s Healthy Eating and Living Study

WHO	World Health Organization
WINS	The Women`s Intervention Nutrition Study
WR	Weighed food record

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1 Introduction

1.1 Diet and cancer

Risk of cancer- a historical view

Migration studies suggest that cancer is, for a large degree, preventable and that environmental factors (i.e. exposing factors) are closely linked to risk of several cancers [1]. Changes in environmental factors, such as smoking, diet, energy intake and physical activity (PA), have been documented among migrating populations along with changes in cancer incidence among different generations [2-4]. Flood *et al.* observed a two-fold increase in the incidence rate of colorectal cancer (CRC) among US-born Japanese men compared to indigenous Japanese men [2]. Moreover, Hemminki *et al.* suggested that environmental exposure the first 2 decades of life influence the cancer progression in both the first and second generation [3]. Apparently, the interplay between lifestyle and genetic background seems to be a central determinant in the cancer process. In 1981, Doll and Peto published the landmark review of the roles of lifestyle, environmental and host factors as causes of cancer [5, 6]. The indirect estimation that 35%, or approximately one third, of cancer cases could be attributable to diet was based on epidemiological studies, resulting in a wide range of uncertainty from 10% to 70% [6]. Blot and Tarone suggested that a more reasonable estimate would be closer to 20% when accounting for the role of specific components of diet [5]. However, considering the importance of life course diet and nutrition on cancer risk, the estimation of 35% still hold true [7]. Tomasetti and Vogelstein [8], World Cancer Research Fund [1], International Agency for Cancer Research (IARC) [9] and others suggested that about 40-50% of cancers are preventable, and that about one third of cancers are caused by dietary factors.

Carcinogenesis

Generally, cancer cells are characterised by mutations among a total of 150-200 cancer driver genes [10, 11], which leads to uncontrolled growth and spread of cells to other tissues. While some of these mutations are inherited, replication errors during stem cell division as well as environmental exposures are the cause of these mutations [1, 10]. When these damaging processes exceed the capacity of repair, and mutations occur in cancer driver genes, cancer may evolve [1, 10]. Cancer cells violate several of the rules ensuring a normal growth and replication, which are postulated as the hallmarks of cancer by Hanahan and Weinberg [11]. These hallmarks describe the phenotypic changes due to mutations and epigenetic factors often involved in cancer development.

Roles of oxidative stress and inflammation in carcinogenesis

Oxidative stress and inflammation are important mechanisms involved in the pathogenesis of cancer [12]. Oxidative stress occurs when there is an imbalance between pro-oxidants (e.g. free radicals) and antioxidants, of which the former dominates, resulting in several oxidative damaging events. Inflammation is the result of a complex series of responses to agents damaging the organism, which when prolonged may progress into a chronic inflammation [12-14]. Antioxidants from the diet may counteract the damages caused by oxidative stress and inflammation. Therefore, nutrition may influence the cellular processes linked to cancer by prevention of cancer development and progression. Thus, inflammation- induced cancers may respond to the activity of nutrients in the diet [1]. In particular, dietary plants and phytochemicals have been shown to regulate the activity of the modulators involved in oxidative stress and inflammation by dampening these processes [15-21]. Moreover, adherence to a prudent diet (e.g. Mediterranean diet) has been suggested to dampen oxidative stress and inflammation [22, 23].

A shift towards food-based dietary focus in cancer prevention research

In the early-1980s, research on cancer prevention was based on the findings from large cohorts suggesting a link between diet and cancer. The search for the causal effects of diet on cancer progression resulted in studies focusing on effects of specific nutrients such as dietary fats, phytochemicals, fibre and selenium [24-28]. However, in the mid-1990s, there was a shift in focus towards intakes of whole foods and lifelong dietary habits in cancer research. In 1997, American Institute for Cancer Research and World Cancer Research Foundation (AICR/WCRF) published the first comprehensive review on research on the effect of diet and lifestyle in cancer prevention, which was updated in 2007 [1]. Moreover, AICR/WCRF constituted an expert panel in 2007, called The Continuous Update Project (CUP), with the mandate to update all scientific results from cohort studies and randomised controlled trials worldwide in order to analyse the scientific evidence of the impact of diet, PA and weight on survival and risk of 17 cancers. In particular, the second updated CUP report for CRC was published in 2017 [29], with new scientific evidence for dietary intakes and PA and risk of CRC. Thus, increased research within this field is important as the incidence of cancers is growing.

1.2 Colorectal cancer

CRC includes cancer in the colon and rectum, as defined by the World Health Organization (WHO) and the International classification of diseases (ICD); ICD-10 classification and the C18-C20 subclasses [30]. About 96% of all CRC are adenocarcinomas which evolves from glandular tissue and the other types are mucinous carcinomas and adenosquamous carcinomas [29, 31]. Adenocarcinoma starts with a polyp which may develop into cancer during a period of many years (i.e. 20-30 years). Adenomatous polyps or adenomas are the ones that most likely develop into cancer; however, most of the adenomas do not become cancerous.

Incidence and survival of CRC

CRC is the third most common cancer in the world, with 1.36 million new cases in 2012 (i.e. approximately 10 % of all cancers)[29]. In Norway, CRC is the second most common cancer type in both men and women with 4343 new cases in 2016 (Figure 1) [32]. The 5-years relative survival has improved from 40% in 1980 to 62% in 2016 [32]. Thus, the population of CRC survivors, i.e. patients living with a CRC cancer diagnose including those who have recovered, is rapidly increasing with the increase in incidence and improvement in survival.

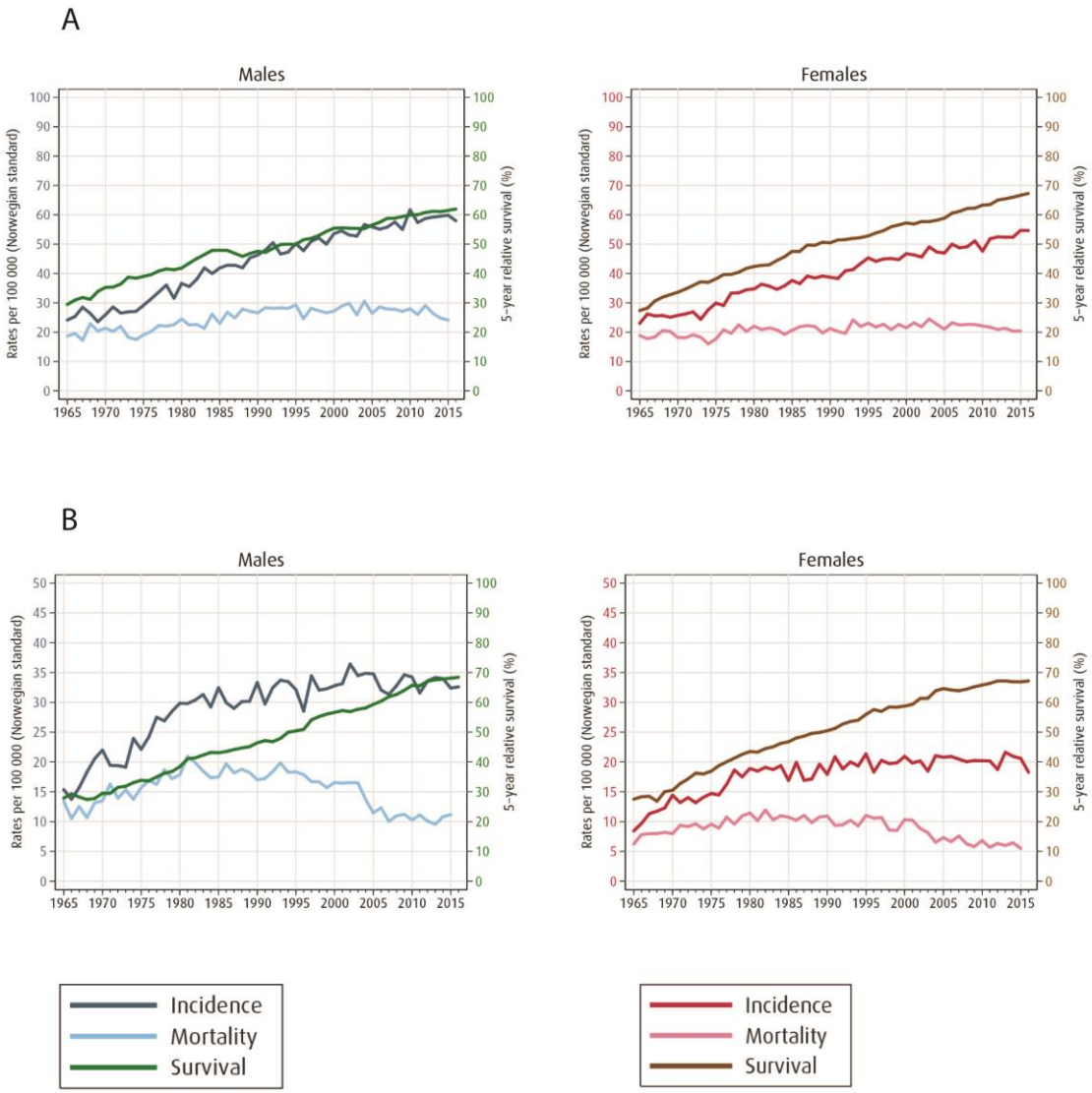

Figure 1. Trends in incidence, relative survival and mortality rates of **A**: colon cancer (ICD-10 C18) and **B:** rectum and rectosigmoid cancer (ICD-10 C19-20) in Norwegian men and women. Figures presented with approval from Cancer Registry of Norway [32].

Risk factors of CRC

Established non-modifiable risk factors for CRC are age, family history of CRC, inherited syndromes (Familial adenomatous polyposis, Lynch syndrome) and inflammatory bowel disease [33].

The modifiable risk factors of CRC are associated with lifestyle factors. AICR/WCRF estimates that 47% of all CRC cases could be prevented with improved lifestyle, such as more PA, higher consumption of foods containing dietary fibre and whole grains, attaining a healthy weight, less intakes of red and processed meat and no alcohol intake [29, 34]. Moreover, comorbidity among CRC patients has frequently been shown. Forty percent of CRC patients have at least one concomitant disease (e.g. hypertension, cardiovascular disease (CVD), diabetes, chronic obstructive pulmonary disease or other malignancies) at the time of diagnosis and increased risk of developing additional comorbidities after CRC diagnosis [35-41].

To summarize, inflammation and oxidative stress has been suggested as major driving forces leading to CRC as well as the frequent comorbidities in these patients [1]. The beneficial effects of a healthy diet [36, 42] may be due to the high intakes of anti-inflammatory and antioxidant-rich foods [15-21] counteracting the progression of these chronic diseases [43, 44].

1.3 Effects of dietary interventions in CRC patients

For the last decades, several intervention studies focusing on the effect of diet, exercise behaviours and body weight status on health related outcomes after cancer diagnosis have been published [42]. Studies focusing on a healthy diet, such as intake of fruits and vegetables, low-fat diets, and energy-restricted diets are increasing and show promising results on survivorship [36]. Most of these studies investigate the effects of several lifestyle behaviours such as healthy foods, healthy weight management and exercise [36, 43, 45]. The majority of the lifestyle interventions include breast and prostate cancer survivors, but only a few are performed among CRC survivors [36, 43, 45].

To elucidate the impact of a healthy diet on disease-free survival and survivorship outcome measurements, there is a need for well-designed clinical trials [36, 43, 45-47]. Few studies have focused on the effect of diet on disease outcomes and survival among CRC-patients [47-51]. High motivation to change lifestyle factors after a diagnosis of chronic disease and maintain them in the long term has been documented in some studies [46, 52]. The 6-months intervention, CanChange [48], found significant changes in multiple health behaviours among CRC survivors 12 month after baseline. In the study of Ravasco *et al.* [50], CRC patients offered individual nutrition intervention during neoadjuvant radiotherapy, showed high compliance to the intervention also at the long-term follow-up of 6.5 years combined with higher survival rates. No intervention studies have investigated the role of dietary intake according to national recommendations on disease outcomes and survival after CRC diagnosis.

1.4 Design of intervention studies in cancer research

1.4.1 Study design in cancer research

In order to find the strongest scientific evidence of an effect of dietary intervention on disease-related outcomes and survival in cancer patients, it is important to choose a design which is feasible and address the research questions.

The most common study designs used in cancer research are observational studies, mechanistic studies and randomised controlled trials, which have different strengths and limitations. Observational studies are often used when estimating distribution of disease in a population and investigating associations between food groups, dietary pattern and health related outcomes (Table 1). The advantages of this design are the ability to include large populations, investigate a range of outcomes and rare

exposures, and to have a high generalisability [53-55]. However, the disadvantages are limited strength of causal inference due to low control of confounding factors in the observed associations [54]. One way to overcome the issue with confounding factors in observational studies, is the use of Mendelian randomisation method [56]. This method is based on the principle that alleles are randomised under meiosis and are therefore independent of confounding factors often found in observational studies. Comparisons between observational studies can be made when knowing the genetic variants associated with an intermediate phenotype of disease in order to reveal the confounding factors [57]. Hence, Mendelian randomisation has a high level of causal inference.

Studies performed in animal models or in cell cultures are used to elucidate the effects of nutrients on cellular or organ level, and are called mechanistic studies. There is low generalisability into humans with this study design. Randomised controlled trials (RCT), however, have the highest strength of causal inference of the treatment effect, as the confounding factors are equally distributed between the study groups by randomisation [54]. All these study designs contribute with different level of evidence of the effects of the exposure (Table 1). Therefore, results from all these study designs are used by expert panel when judging the scientific evidence for effects of nutrients and diet on progression of diseases, such as WCRF/AICR and Norwegian Nutrition Council [1, 29, 58, 59].

Table 1. Time aspects of study designs in cancer research and strength of causal inferences.

Adapted from Margetts *et al.* [54] and Veierød *et al.* [60].

Design of studies	Time			Strength of evidence
	Past	Present	Future	
Observational studies				
Ecological studies		Exposure and outcome measured at group level		Association on group level- development of broad hypotheses
Cross-sectional studies		Exposure and outcome measured once, without prior knowledge. Determine prevalence of exposure or disease		Observed association-development of hypotheses
Case-control studies	←	Define cases and controls from same population, retrospective exposure		Indicate causal association
Cohort-studies Retrospective	←	Define cohort, collect existing data on exposure and endpoints		Indicate causal association
Cohort-studies Prospective		Define cohort, exposure recorded before endpoint	Endpoints measured →	Indicate causal association
Mendelian randomisation		Define genotype which affect disease status indirectly, exposure recorded before endpoint	Endpoints measured →	Causal effect
Mechanistic studies				
Mechanistic studies		Investigating effects of biologic or chemical events on processes in animal-model or cell-culture in order to shed light on specific mechanisms in diseases	Exposure modified, endpoints measured, or observation of associations of mechanisms →	Indicate causal association
Experimental studies				
Randomised controlled trial		Define population, randomise subject to study groups without prior knowledge on exposure or endpoints	Exposure modified, endpoints measured →	Confirmed causal association

1.4.2 Randomised controlled trials in cancer research

RCT is the ‘golden standard’ of study design when testing intervention effects. However, RCTs are challenging for intervention studies testing effects of diet on developing chronic diseases, such as cancers, due to the long-time perspective. Additionally, RCTs are very resources demanding due to large study cohorts, study medication and follow-up procedures on every patient. Consequently, observational and mechanistic study designs dominate in the field of cancer prevention research.

RCTs have an optimal design to test hypotheses and effect of a nutrient or food given to the intervention group [61]. When planning a RCT it is important to consider the time-frame of the study, as it depends on the expected intervention effect on the outcome. RCT designs may include short-term designs like a postprandial study looking at the immediate effect of nutrient intake after some minutes or hours, or long-term designs over months or years when studying effects of dietary intakes on disease-free survival or overall survival. It is important that the duration of the intervention and the follow-up cover the expected time of changes in the outcome measures and at the same time do not lasting more than needed for ethical reasons.

Control group in RCTs

Intervention studies which include a control group (i.e. RCT) increase the confidence of an intervention effect, and is therefore rated as the golden standard with the highest level of evidence [54]. Control group in nutrition research has been subject to debate due to the challenge of fulfilling the traditionally placebo criterion for placebo foods. Thus, a central assumption of the optimal RCT design is violated compared to typical studies in pharmaceutical sciences. However, in nutrition research, the control group may receive no intervention, standard of care or a specific treatment depending on the outcomes of the intervention.

Randomisations

In RCTs, the allocation of participants to interventions is performed using a random procedure such as the use of opaque, sealed and sequential numbered envelopes or computer-generated randomised allocation. Randomisation ensures groups with similar prognosis, no selection bias and equally distributed confounding factors between the groups [60, 62, 63]. In clinical intervention studies involving patients, recruitment of patients may be challenging due to accessibility of the number of eligible participants needed for fulfilling the power of the effect on outcome in the study. The result might be successive recruitment over a long time-period and similar numbers of participants allocated to each study group at any time-period is important.

In simple randomisation, the participants are allocated to either a treatment- or control group according to a fixed randomisation list. However, simple randomisation may fail to assign equal number of participants in each group and may also create an imbalance in known factors influencing prognosis or response to intervention [60, 64].

A block randomisation will ensure equal numbers of participants in each study group. The size of a block varies from 4, 6 or higher of which the participants are randomly allocated to one of the study groups within that block. For instance, a block of 4 means that the participant may be allocated to one of the two study groups as depicted by the sequence of the study groups in the block (i.e. 1212, 1122, 2121, etc.). The size of block may also differ in random time-periods to avoid predictability of the allocation (i.e. either a block size of four or six) [60, 64].

Another strategy to prevent imbalance between the study groups is to randomise the participants according to stratification factors known to influence prognosis or

response of intervention, such as age, sex, BMI or treatment regime. Stratified randomisation increase power of small trials by preventing Type I error and make it possible to perform interim analyses in large studies [65].

Blinding

In clinical trials, blinding may be an appropriate method to avoid biased results particularly when assessing subjective outcomes [66, 67]. Blinding can be used when assigning participants to the intervention by withholding information about the allocated study group, which is referred to as allocation concealment [66]. In randomised controlled trials, the term blinding refers to that participants, data collectors or research managers are unaware of the treatment allocation. Double-blinding is when both participants and researchers are unaware of the allocation, whereas single blinding is when the patient is blinded to the allocation. However, blinding may not always be possible or necessary, such as in studies with objective outcomes (i.e. disease-free survival or overall death), and this is called open-blinded studies [63]. For example, blinding is not possible in intervention trials involving individualised dietary counselling. However, it may be possible to blind data collectors when analysing outcome measures [66, 67].

Designs of randomised controlled trial

Parallel or cross-over study design are the most common types of RCT. Participants in parallel group studies receive only one of the interventions and are equally followed up from baseline to end of intervention. Effect of outcome in the intervention group is compared to the outcome in the control group (i.e. between-participants comparison). Parallel study designs are preferred in long-term interventions and when studying behavioural factors influencing prognosis of disease and health, such as weight, BMI, cognitive function or dietary behaviours [60, 64].

Cross-over study design is a repeated measurement design in which the participant receives (by randomisation) all interventions in a pre-defined order and with a certain time-period between each intervention (wash-out) [60]. Duration of the wash-out period should last long enough in order to avoid carry-over effects from one intervention to the other. A run-in period is recommended prior to the interventions in order to minimise the differences between the participants that may influence the intervention effects on the outcome. Each participant functions as their own control, which is advantageous in particular for two reasons; firstly, the comparison between interventions is made within participants that will improve the precision of an intervention effect as the participant characteristics are constant for all treatment groups. Secondly, it usually needs a smaller sample size compared to a parallel design with similar level of statistical power [60]. The cross-over design may be effective in short-term dietary interventions, such as postprandial studies. A disadvantage of cross-over design might be a longer total duration of the study compared to a parallel design, due to the sum of all interventions including wash-out periods.

Research question and power calculation in randomised controlled trials

Defining the research question is first priority in designing the intervention study and should pose both primary and secondary questions. The research questions should specify the population, the intervention and the outcome measurements. The design should also be innovative, approachable and answerable, and be expressed as a null hypothesis stating that there is no difference between the study groups [63]. Designing the intervention in detail is important and is framed by the research question, effect on outcome, study design and available resources. It should specify whether it should include whole foods, intake of specific foods, nutrients or dietary pattern. Moreover, it should also define the way participants should receive the intervention strategies, i.e. home-based intervention with foods given as a supplement in their daily life or a whole diet given to participants in an institution etc. When planning a study, it is also important to define the eligible criteria describing

the participants to be included in the study. These could include demographic variables as well as lifestyle factors.

Having phrased the research questions and the clinical meaningful change in the outcome variables, this information is used in power calculation in order to estimate the number of participants that should be recruited to the trial. Sample size estimation needs also to take into account non-compliance and drop-out rate as well as the variability of the meaningful difference in the outcome variable. This variability may be found in other published similar studies or from a pilot study performed prior to the planned intervention.

Study protocol

All intervention studies must specify the aims of the study, intervention strategies, study population, data handling and power calculation in a protocol. This protocol needs to be approved by a local ethical committee and registered in a publicly accessible database before inclusion of the first participant to the study, as stated by the World Medical Association`s Helsinki Declaration. All participants invited to the study have to sign an informed consent, which also need to be approved by the ethical committee prior to the onset of study. The study protocol should also specify methods of recruitment of participants, inclusion criteria, and procedure for discovery of any adverse events for the participants, outcome measures and standard operating procedures (SOPs) for all dietary assessments, biological samplings, measurements and statistical considerations [63].

1.5 Dietary assessment methods

For intervention studies assessing the effects of dietary exposure on health outcomes, it is important to choose the most proper dietary assessment method which give valid estimates of dietary intakes with the least error in the

measurements. All dietary assessments are subject to measurement errors; therefore it is important to be aware of this when interpreting effects of dietary intake on health outcomes. Some dietary assessment methods gives valid estimates on group level and are able to rank individual intakes within that group, whereas other assessment methods are more suitable on individual level. For instance, in observational studies characterising dietary intakes in large populations, the most frequent used method is questionnaires [54, 55]. Since epidemiological studies dominate within medical research, questionnaires also dominate as dietary assessment methods and thus have the longest tradition of dietary assessment method [54, 55].

Dietary assessments methodologies have been developed along with the changes in study design, technology and statistical analyses since the mid-20th century [64]. For instance, a study may choose to develop a questionnaire from basic principles, or adapt it from existing questionnaires [68]. The review of Cade *et al* [68] found that about 54% of the included validation studies were adapted from an existing questionnaire, of which the NCI/Block Health Habits and History Questionnaire and the Harvard Semi-quantitative Food Frequency Questionnaire dominated [55, 69]. Refinement of dietary assessments needs to be evaluated against well-established methods with known strengths and pitfalls.

Generally, dietary assessment methods used in nutritional research today can be classified according to the time-frame of data collection, i.e. retrospective or prospective assessment methods.

1.5.1 Retrospective dietary methods

When investigating associations between dietary habits or foods usually eaten and chronic diseases, retrospective dietary assessment methods are the most appropriate method to use. Food frequency questionnaires (FFQ) and 24-hour dietary recall interviews are the most common retrospective methods. The main advantages of these methods are that they are quick to complete for the respondents and does not require the respondents to be very motivated [54].

24-hour recall

The 24-hour dietary recall is an open-ended method asking for dietary intakes the previous 24 hours or day. It may be interviewer-administrated or self-administrated, and structured in a useful way to help the participant to remember the dietary intake. The advantages are detailed information of dietary intakes including portion sizes, low respondent burden and non-respond bias, and no effect on eating behaviour, since the information is retrieved after the recording day [54, 55]. However, interviewer-administrated 24-hour recall is expensive and repeated interviews (i.e. how many days to include, include week-days and weekend-days, different seasons etc.) are required to measure usual dietary intakes [55].

Food frequency questionnaire

The most common type of FFQ is the closed-ended FFQ consisting of a specified food list and fixed frequency responses [62, 70]. FFQs are used to rank individuals according to dietary intakes and may generate data on absolute dietary intakes on group level [62, 70]. The design of the FFQ varies according to the objective of the study and the kind of dietary data needed, such as which food items or nutrients to be included, portions sizes, frequency categories, length of questionnaire and duration of registration period (i.e. the last few days, weeks, months or year) [54, 55, 68].

Generally, FFQs assess frequency of food intakes and portion size of the food consumed (i.e. semi-quantitative), but some are restricted to the frequency of intake only (i.e. qualitative) [54, 55, 68]. FFQs are normally self-administrated, although interviewer-administrated or telephone-administrated FFQs also occur occasionally, which have shown higher correlations in relation to a reference method [68]. However, reporting error may be reduced in self-administered FFQs with a clear instruction and use of relevant examples, such as pictures of portion sizes. FFQs rely on memory and the participant's conceptualism of portion size and frequency of intake [54, 55].

Overall, FFQs should include foods which are eaten often, foods that have substantial content of nutrient of interest and the use of food must vary from person to person to be able to rank subjects in food intake [55, 62]. Self-reported dietary assessment tools (i.e. FFQ) play a major role in characterizing dietary intakes in several large studies, such as The Dietary intake in the European Prospective Investigation into Cancer and Nutrition (EPIC) study [71], The Norwegian Women and Cancer Study (NOWAC) [72], the Norwegian nationwide survey (NORKOST) study 1 and 2 [73] and The Women's Health Initiative Dietary Modification Trial [74, 75]. Moreover, in the large health survey performed in a Norwegian population of Nord-Trøndelag county called Nord-Trøndelag Health Study (HUNT study), participants reported dietary intakes and time in PA by completing several FFQs (e.g. HUNT 3) [76, 77].

1.5.2 Prospective dietary methods

Prospective dietary assessment methods are used in studies when the aim is to characterize current dietary intakes. For instance, food diaries or food records are the most common prospective dietary assessments tools, and may involve either weighing of foods or reporting portions in household measures (i.e. open-ended), or

reporting frequency of pre-quantified foods (i.e. closed-ended such as pre-coded food diary) [54, 55]. The advantages of the open-ended methods are the direct recording of dietary intakes (when used in repetitive periods) with no reliance on memory and no restriction in number of food items included. Moreover, open-ended records give detailed information of food consumption, capture daily variations when used in intakes and contribute to improved estimations of portion sizes, which may result in less errors and variation in the estimates. However, the method is expensive for the researchers and may be burdensome for the respondents, which also depends on the number of recording days [54, 55].

1.6 Physical activity assessment methods

Reliable and valid methods in monitoring PA are needed in public health as well as intervention studies aiming at improving the level of PA [55, 78]. There are several methods for measuring PA and choosing the most appropriate method depends on the aim of the survey.

1.6.1 Retrospective physical activity methods

Questionnaires

Self-administered assessments tools, such as retrospective questionnaires, are most common used in public health and studies focusing on PA at population level. As with dietary behaviour, PA is a complex behaviour consisting of intensity, duration and frequency. Therefore, in self-reported methods there are similar measuring errors, such as day-to-day variation, reliance on memory and participant's conceptualism of intensity, duration and frequency of PA [79]. The most common method to assess self-reported PA is questionnaires [80, 81], and more than 30 PA questionnaires have been developed and validated over the past 2 to 3 decades [55]. Energy expenditure

is an important risk factor in chronic diseases and is influenced by the level of PA. Data from PA questionnaires can be used to calculate energy expenditure by multiplying time spent in each activity expressed in metabolic equivalent (METs), of which 1 MET is equivalent to resting metabolic rate (RMR) [82]. PA questionnaires share the same advantages as the FFQ in dietary research, such as assessing long-term habitual PA patterns, low burden for participants to complete and low costs for the researchers. However, the questionnaire suffers from random and systematic errors, such as over-reporting of PA and underreporting sedentary behaviour.

Short- term recall

Another retrospective assessment tool used in monitoring habitual PA level is the open-ended short-term recall, ranging from 24-hour to 1 month, of which the participants are interviewed by the researcher. When estimating long-term PA several recalls are needed due to the daily variations. The disadvantages of short-term recalls are the reliance on memory, the burden for the participants and the cost for the researchers.

1.6.2 Prospective physical activity methods

PA record

Another open-ended physical assessment tool is the PA record [55]. This prospective method require recording of type, duration and intensity of activity right after completion, and therefore can be considered as a reference method. They are burdensome for the participants and may influence the participants PA behaviour, which however may be reduced by a digital activity log [55].

Objective methods

During the last decades, use of the more detailed and accurate objective prospective methods in recording PA have increased and gives valid and reliable data on intensity

of PA and energy expenditure [83]. The most common and well-established methods are indirect calorimetry, doubly labelled water, direct observation, heart rate telemetry, and movement sensors [55, 84]. Since objective methods have no issues of recall bias and give more detailed and precise estimates, they are often used as a reference method in validation of self-administrated methods.

Activity monitors have the advantages of being non-invasive with no influence on activity behaviour and therefore well suited for monitoring physical activities in free-living individuals. The more advanced motion sensor generates data on heat flux, galvanic skin response, multi-axis accelerometer and skin temperature in addition to data on intensity, duration and frequency of physical activities. Moreover, the co-predictors such as weight, height, birth date, sex and smoking status can be added by the researcher and integrated into algorithms used by the software providing estimates of energy expenditure expressed in METs [55, 85]. However, these activity monitors are expensive and time consuming for the researcher, particularly when recording PA in larger populations [84].

1.7 Validation of dietary and physical activity methods

1.7.1 Validation of dietary methods

Validity refers to the degree to which a measurement is a true and accurate measure of what it purpose to measure [55]. The true dietary intake is difficult to assess with questionnaires, recalls or records without errors, due to the existence of bias and errors in all of the methods. Therefore, when evaluating a new dietary method, we measure the relative validity against another dietary method accepted as a reference method. Common reference methods are objective methods, such as dietary records, biomarkers of food intake and doubly-labelled water [54, 55].

In validation of questionnaires, open-ended diet records are the most common reference methods used with least degree of correlated errors [68]. None of the methods measures the absolute true intake, but they are able to discriminate dietary intake among individuals. When using open-ended records as the reference method to measure usual daily dietary intake, it is important to include a sufficient number of days in order to measure average intakes [68].

Measuring errors

Measuring errors may occur both on individual and group level and can be categorized into random and systematic errors. Random errors within individuals is often related to day-to-day variation of dietary intake particularly for seldom eaten foods, whereas systematic individual errors often applies to the method itself such as portion sizes or food list [54, 55]. Random errors between individuals is mainly the difference between individual`s intakes and the population`s intake which may influence the observed standard deviation of a population (i.e. larger than the true standard deviation). The consequences may be over- or underestimation, which attenuates the dietary effect of a health outcome [64]. Errors in questionnaires are often related to memory, knowledge of portion sizes and understanding of the questions. These errors are less associated with the errors in open-ended records, in the way that open-ended records are neither depended on memory nor on the perception of portion sizes. However, the possible related errors between those two methods may be associated with the food composition database. For example, this may happen when the recipes of a food dish reported by the individual in the open-ended record are calculated from a fixed portion size in the same database as the portion sizes of the different food items in the questionnaire [54, 55].

Timing of test- and reference methods

When designing a validation study, timing and sequence for the test- and reference method is important [68]. The test method should be administrated prior to the

reference method, avoiding any learning effects from the reference method [54]. Time frame should also reflect the aim of the test-method, whether assessing usual diet over a long period of time or dietary intake in recent time, such as the last month. Validity of a test-method may differ in other settings or population and additional validity should therefore be considered [54, 55, 64, 68].

Confounding factors in reporting dietary intakes

Different reporting among sex is well documented [54], therefore, validation should be stratified on sex. Moreover, age may be another confounding factor important to take into account, particularly among children and adolescents but not so frequent among adults. Elderly may experience difficulties in reporting due to altered memory and fatigue [54, 55, 86-93].

1.7.2 Validation of physical activity methods

Validation of PA questionnaires against open-ended PA dairies or logs faces similar challenges as for dietary assessment tools. Direct measures of PA are common to use as reference method in validation of questionnaires. In particular, accelerometers and monitor sensors are the most common used direct measurement, which is well-established and validated methods for both time in PA and energy expenditure [78, 94].

1.8 The Norwegian Dietary Guidelines and Colorectal Cancer Survival (CRC-NORDIET) study

The risk of developing CRC is causally related to low intake of whole grains, foods containing dietary fibre, dairy products and high intake of red and processed meat, alcoholic drinks as well as body fatness [29]. All of these risk factors are included in

the Norwegian Food Based Dietary Guidelines (Norwegian FBDG) published by the Health Authorities in Norway [59]. These guidelines focus on prevention of chronic diseases in the general population and have a broader perspective than the risk factors related to CRC. Instead of only focusing on dietary factors causally related to risk of CRC, we have in the CRC-NORDIET study chosen to focus on a complete diet that is consistent with the Norwegian FBDG since CRC patients have increased risk of life-style related co- and multi-morbidities. We suggest that adherence to the Norwegian FBDG post-diagnosis might improve cancer progression as well as comorbidities and total survival among these cancer patients.

There are no previous intervention studies investigating the role of dietary intake according to national recommendations on disease outcomes and survival after CRC diagnosis. Therefore, we developed and initiated the Norwegian Dietary Guidelines and Colorectal Cancer Survival (CRC-NORDIET) study in year 2012 at Department of Nutrition, University of Oslo in Norway (Paper I [95]). The multicentre randomised controlled two-armed CRC-NORDIET study investigates the effects of the Norwegian FBDG on disease-free and overall survival among CRC survivors. In order to estimate the participant's adherence to the Norwegian FBDG during the study, we developed and validated a short food frequency questionnaire (NORDIET-FFQ). Moreover, PA is self-reported by the completion of NORDIET-FFQ and the HUNT-PAQ questionnaire and objectively measured by a PA monitor.

2 Aims of the thesis

The aim of this thesis was to design and establish the RCT ‘The Norwegian Dietary Guidelines and Colorectal Cancer Survival (CRC-NORDIET) study’ which investigate the effect of diet intervention on survival among CRC patients. The aim was also to develop and validate dietary intake and PA assessment tools used in the CRC-NORDIET study. More specifically, the aims of the present PhD thesis were:

- To design and establish a RCT investigating effects of dietary intervention according to the Norwegian FBDG on disease-free and overall survival among patients with localised CRC.

- To develop a new short food and PA frequency questionnaire (NORDIET-FFQ) designed to estimate adherence to the Norwegian FBDG.

- To validate the NORDIET-FFQ using weighed food records and PA monitor as reference methods.

3 Design and subjects

3.1.1 Design of CRC-NORDIET study

Study design

The aim of the CRC-NORDIET study is to investigate the effects of a healthy diet on survival among CRC patients. The CRC-NORDIET study is a multicentre randomised controlled, parallel two-armed intervention trial, as described in detail in Paper I. Five hundred CRC patients are randomised into one of the two study arms (250 in each arm) (Figure 2). The intervention group receives an intensive dietary intervention, whereas the control group follow the hospitals standard care of dietary advice. Both study groups are offered equal intervention on PA. All patients in the CRC-NORDIET study are intensively followed up the first year of intervention, and thereafter moderately followed up for additional 14 years (Figure 2).

Recruitment and randomisation in CRC-NORDIET study

Patients are recruited from Oslo University Hospital and Akershus University Hospital, two hospitals within the South-Eastern Norway Regional Health Authority, and they are invited to the study 3-4 weeks post-surgery. Eligible patients to the CRC-NORDIET study are screened from hospital surgery lists and medical records in cooperation between the research investigators and hospital personnel. All patients accepting the invitation signs the informed consent prior to the study baseline, which is within 9 months from surgery. Patients are invited to the study successively, reflected by the surgery lists at the hospitals. Computer generated block randomisation, with block size four, was used to allocate the subjects to one of the two study groups at each hospital. Double-blinding will be performed when analysing data collected from patients (Paper I).

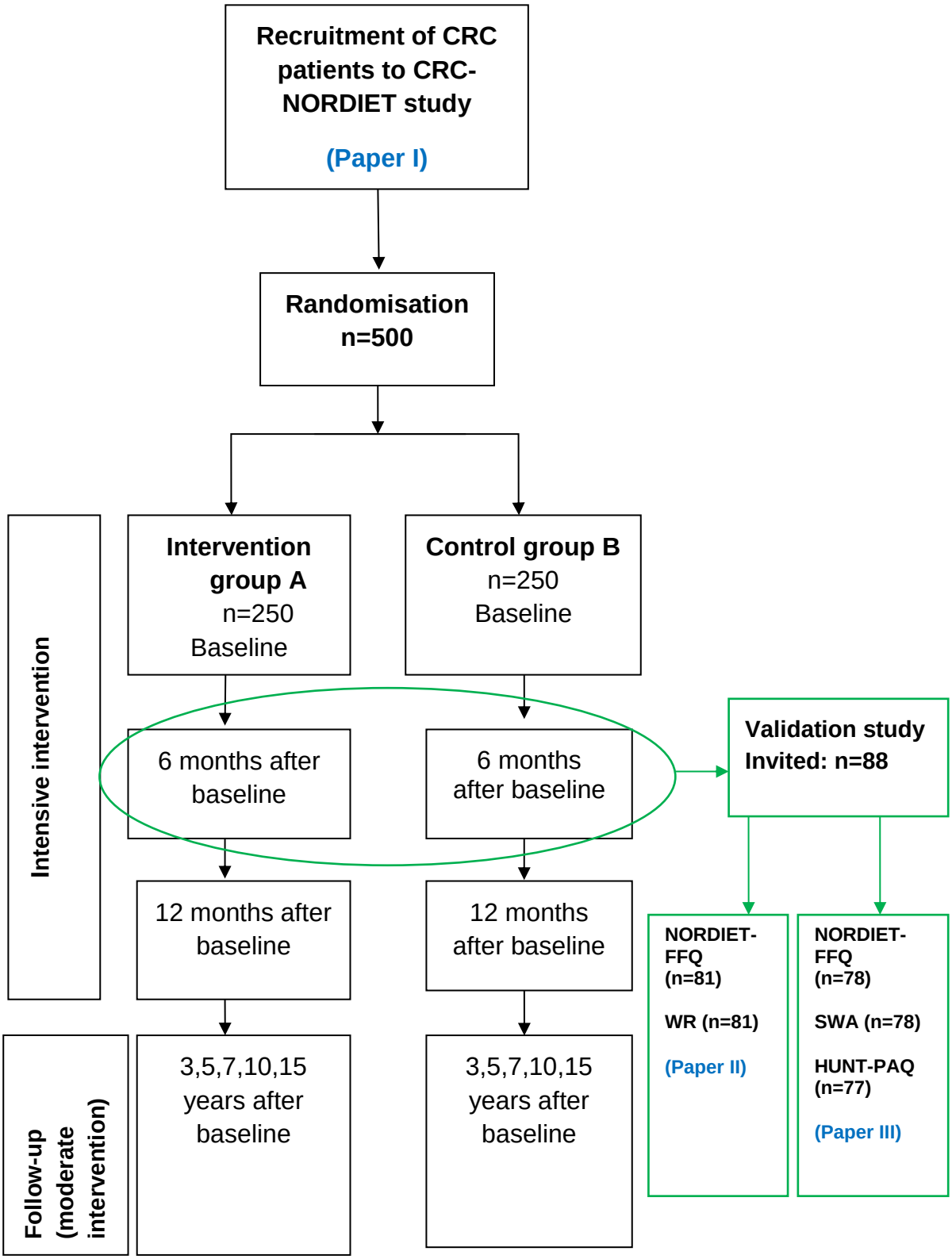

Figure 2. Study design and flow of participants in the CRC-NORDIET study and validation study

Collection of data in CRC-NORDIET study

The CRC-NORDIET study database accumulates a great body of data from several questionnaires, objective measures of body composition, anthropometric measures, biological samples, blood pressure, PA, physical function and health registries. In addition, samples for biomarker analysis as well as samples for characterising CRC progression and gut microbiota are collected. Similar data and measurements are collected from both study groups at each visit at the study centre (Figure 3). Additionally, data from medical records and health registries are collected when needed in sub-studies of the CRC-NORDIET study.

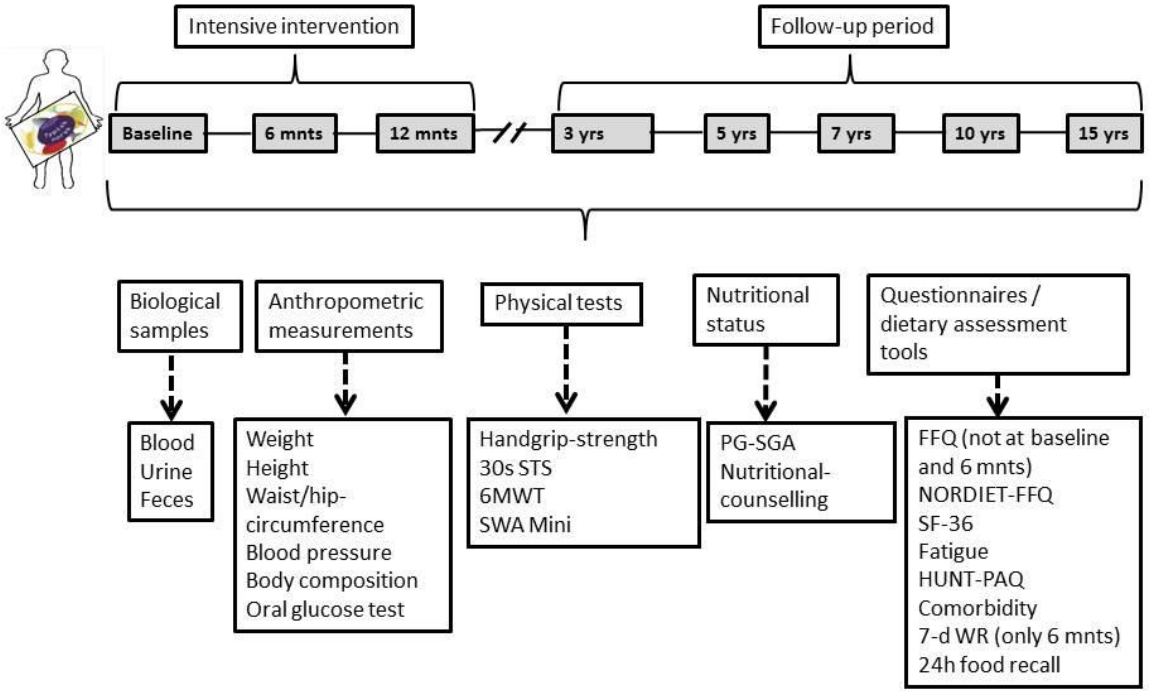

Figure 3. Timeline of data collection in the CRC-NORDIET study. All measurements and recordings are performed at each study visit.

3.1.2 Design of validation study

A new short semi-quantitative food frequency questionnaire (NORDIET-FFQ) aiming at estimating adherence to Norwegian FBDG was developed and validated (described in Paper II and Paper III). The validation study was designed as a sub-study of the prospective randomised controlled trial, CRC-NORDIET study (Figure 2).We validated the ability of NORDIET-FFQ to estimate dietary intakes and PA according to the Norwegian FBDG in CRC patients.

Methods in the validation study

Participants completed the self-administered NORDIET-FFQ during the 6-months visit at the study centre, of which completeness was checked by the researchers. Dietary intakes estimated by the NORDIET-FFQ was validated against a 7-days weighed food record (WR) (i.e. reference method), which were completed at home within 2 weeks (Paper II, Supplementary file 3).

The NORDIET-FFQ also contained two questions about PA in two intensities (i.e. moderate PA (MPA) and vigorous PA (VPA)) estimated in pre-defined epochs of frequency per week and duration in minutes (Paper III). In addition, the participants reported PA from a well-established questionnaire called HUNT-PAQ [76] at the study centre during the same visit (Paper III). The participants received a PA monitor, SenseWear Armband Mini (SWA) [85], used as a reference method against self-reported PA from the two questionnaires. The participant wore the SWA for 7 consecutive days and was then returned by mail to the study centre (Paper III, Supplementary file 4).

3.1.3 Subjects in the CRC-NORDIET study and in the validation study

Men and women aged 50-80 years old, with non-metastatic CRC (ICD-10 18-20), and staged I-III (i.e. locoregional disease without metastasis) according to the TNM staging system [96] are invited to the CRC-NORDIET study [95] (Paper I, Table 2).

Table 2: Inclusion criteria for participants to the CRC-NORDIET study and the validation study

	Inclusion criteria
Paper I	- men and women 50 -80 years of age - newly diagnosed primary invasive colorectal cancer (ICD-10 18-20) staged I-III - no colorectal adenoma, carcinoid, abdominal carcinomatosis or sarcoma. - able to read and understand Norwegian - no diagnosed dementia, or altered mental status - able to follow the dietary intervention , e.g. not permanently institutionalised or total parenteral nutrition - not participation in another study conflicting with the intention of the CRC-NORDIET study
Paper II	- sub-population of CRC-NORDIET study from both study groups - completed NORDIET-FFQ and WR
Paper III	- sub-population of CRC-NORDIET study from both study groups - no pacemaker - completed NORDIET-FFQ, HUNT-PAQ and SWA

4 Summary of papers

Paper I:

The Norwegian dietary guidelines and colorectal cancer survival (CRC-NORDIET) study: a food-based multicentre randomised controlled trial

CRC is one of the most common cancers worldwide and the incidence is increasing. It is a preventable cancer and according to the World Cancer Research Fund 47% of all CRC would have been prevented with a healthy lifestyle. Although, the preventable effects of diet are well documented, little is known about the health effects of diet post-diagnosis. Consequently, there are no specific dietary guidelines for CRC survivors. In order to broaden the knowledge of long-term effects of diet on health related outcomes post-diagnosis among CRC survivors, we designed the Norwegian Dietary Guidelines and Colorectal Cancer Survival (CRC-NORDIET-study) study which is presented in Paper I. The primary objectives were to investigate the effect of a healthy diet in accordance with the Norwegian food-based dietary guidelines and to focus on dampening inflammation and oxidative stress on disease free survival and overall survival among colorectal cancer survivors. In addition, several secondary outcomes focusing on both survival - and non-survival related outcomes were included. The RCT design was chosen due to the need of isolating the effect of diet on the outcomes and controlling confounding factors. Moreover, since it takes time to change dietary behaviour and measure effects on chronic diseases, the duration of the intensive dietary intervention last for as long as 12 months, with a subsequent 14 years of following up period. The study includes CRC patients with the highest preventable gain on outcomes in the long term. Thus, men and women aged 50-80 years, with non-metastatic CRC (ICD-10 18-20), and staged I-III according to the TNM staging system are invited to participate in the study. The study centre is located at the Department of Nutrition, University of Oslo, and patients are recruited from two hospitals within the South-Eastern Norway Regional Health Authority.

Paper II:

Relative validity of a short food frequency questionnaire assessing adherence to the Norwegian dietary guidelines among colorectal cancer patients

As part of the ongoing dietary randomised controlled trial (CRC-NORDIET study), focusing on health effects of a diet in accordance with the Norwegian Food Based Dietary Guidelines among colorectal cancer survivors, a new dietary assessment tool estimating adherence to the guidelines was needed. Therefore, we developed a new short food frequency questionnaire (NORDIET-FFQ) estimating adherence to the Norwegian food based dietary guidelines, as presented in Paper II. Eighty-one CRC-patients from both study groups in the CRC-NORDIET study were included in the validation study. The NORDIET-FFQ contained 63 dietary items which was evaluated against a 7-days weighed food record as the reference method. The NORDIET-FFQ was on group level able to estimate intakes of fruits, vegetables, unsalted nuts, fish, fatty fish, high fat dairy products, non-processed meat, processed meat, red meat, water, sugar rich beverages, alcoholic drinks and sugar- and fat rich foods. Moreover, ranking of individual intakes were evaluated as good for estimated intakes of fruits, fruits and vegetables, unsalted nuts, whole grains products, sugar-rich cereals, fish, fatty fish, dairy products, red meat, water, sugar rich beverages, alcoholic beverages and sugar- and fat rich foods. However, poor ranking ability was observed for intakes of non-processed meat, processed meat and vegetables. Importantly, the NORDIET-FFQ showed a good ability in identifying those patients in need for dietary counselling for the foods which are known to modulate the risk CRC, such as fruits, vegetables, unsalted nuts, whole grains, low fat dairy products, processed meat, water, alcoholic beverages and sugar- and fat rich foods.

Paper III:

Validation of two short questionnaires assessing PA among colorectal cancer patients

The Norwegian Food Based Dietary Guidelines contains recommendations of PA defined as moderate-to-vigorous PA (MVPA) or MPA of at least 150 min/week or VPA of 75 min/week. Therefore, in order to estimate PA among the study participants the new NORDIET-FFQ developed in the CRC-NORDIETs study, included 2 questions concerning two intensities of PA, i.e. moderate and vigorous PA. In addition, a questionnaire focusing solely on PA and adapted from the HUNT3-study was used in the CRC-NORDIET study to further estimate level of PA as well as sedentary time (ST). This paper presents the results from the validation of the two questionnaires and their ability to estimate adherence according to the national recommendations of PA (Paper III). Participants from the CRC-NORDIET study were included in the validation study, of which 78 and 77 completed the NORDIET-FFQ and the HUNT-PAQ, respectively. Self-reported PAs from both questionnaires were evaluated against the objective monitor SenseWear Armband Mini (SWA) as the reference method, worn by the participants for seven consecutive days. Time in MVPA and MPA measured by the SWA was similar to the time estimated with the NORDIET-FFQ, in contrast to the HUNT-PAQ which under-estimated both time in MVPA and MPA. However, the NORDIET-FFQ was unable to rank individual time in MVPA or MPA, whereas time in MPA and ST were acceptable ranked among women only with the HUNT-PAQ. While there was almost no under-reporting of MVPA, MPA was more under-reported with the NORDIET-FFQ. All intensities were under-reported by the HUNT-PAQ to a greater extend as compared to the NORDIET-FFQ. The HUNT-PAQ was able to identify those in need of counselling to MVPA and MPA, whereas the NORDIET-FFQ identified those who fulfilled the recommendations of MVPA and MPA.

5 Discussion

Increased knowledge about the effect of diet on disease-free and overall survival in CRC patients is needed. The objective of this thesis was to design a randomised dietary intervention study, which we named The Norwegian Dietary Guidelines and Colorectal Cancer Survival (CRC-NORDIET) study. The study investigates whether a diet aimed at dampening inflammation and oxidative stress and in full accordance with the Norwegian Food Based Dietary Guidelines (Norwegian FBDG) will improve disease-free and overall survival as well as a number of secondary outcomes in CRC patients. Another aim of the thesis was to validate in CRC patients a short semi-quantitative food and physical activity frequency questionnaire (NORDIET-FFQ) developed for this study and the well-established HUNT-PAQ questionnaire.

5.1 Study design and subjects

5.1.1 CRC-NORDIET study

Duration of study

Studies aiming at dietary changes in patients with chronic diseases need often an extensive intervention with long-term follow-up as diet effects may be moderate (compared to drugs) and it may take considerable time to develop any health effects on chronic diseases. In order to maintain dietary changes in the long-term, it is of great importance to design an intensive intervention which lasts for about 12 months and with a subsequent long-term (i.e. several years) and intensive following up period [42, 45, 46, 52, 97, 98]. Additionally, long-term following up is needed to reach adequate power to detect intervention effect. Therefore, the CRC-NORDIET study is designed with a long (i.e. 12 months) and intensive intervention and with a long-term maintenance period with follow up of 15 years.

Recruitment of subjects and randomisation in CRC-NORDIET study

Successive entry of subjects into intervention study is common in clinical trials with cancer patients; hence block randomisation is also often used when allocating subjects to the study groups [48, 99-101]. The advantage of using block randomisation prior to baseline is to ensure equal distribution of patients within both study groups at any time-point of the intervention. Additionally, the successive entry of participants to the study reduces the effects seasonal variation or systematic changes during time. Due to the nature of the intervention, there is no blinding at allocation but a concealed allocation. Neither the patients nor the research investigators responsible for the recruitment of patients are aware of the randomisation sequence at the time of invitation. All patients are informed about their allocation to a study group after signing the informed consent (i.e. at baseline), ensuring that their willingness to participate is not influenced by their allocated study group (Paper I). The concealed allocation of patients to study group also prevents selection bias.

Travel distance to study centre has been shown as an important barrier among cancer patients to participate in intervention studies involving face-to-face counselling [45]. Thus, several home-based lifestyle interventions such as the RENEW, FRESH-START, CanChange and NC STRIDES trials, have been developed [48, 97, 98, 102]. Since the CRC-NORDIET study includes many visits at the study centre at the University of Oslo, travel distance may restrict participation in the CRC-NORDIET-study. To counteract this effect, all participants receive reimbursements for travel expenses to the study centre.

Control group

The CRC-NORDIET study is not a placebo-controlled RCT, but confounding factors are equally distributed between the study groups due to the randomisation (Paper I). The control group in the CRC-NORDIET study are given conservative information on

recommended diet as in usual care, which is standard practice in other randomised controlled trials performed among cancer patients [52, 99], such as WINS [103], WHEL [104], CanChange [48] and the dietary intervention among CRC patients conducted by Ravasco *et al.* [50, 101].

Effects of lifestyle (i.e. diet, PA, smoking) on survival in cancer patients have been investigated in several studies [36, 42, 43, 45, 48, 98, 100, 102, 105-108]. However, effects of diet and PA are integrated and difficult to separate. Therefore, we decided to include general advice on PA both in the control and the intervention group in the CRC-NORDIET study in order to isolate the effect of diet on the endpoints. Assessment of PA is performed in the same way in both study groups using objective PA monitors, physical tests (i.e. handgrip strength, 30-second sit-to-stand test, 6-minute-walking-test) as well as self-reported PA assessment tools (i.e. questionnaires).

5.1.2 Validation study

Since this was the first intervention trial focusing on health effects of the Norwegian FBDG among CRC patients post-surgery, there was a need for a new dietary and PA assessment tool measuring adherence to these guidelines. In the validation study, the test method (i.e questionnaire) was completed prior to the reference method, thereby avoiding any learning effects from the reference method, as recommended by Michael Nelson in Magretts *et al.*[54]. Moreover, the questionnaire was a retrospective method assessing usual dietary intake and PA in recent weeks (i.e. the last 1-2 months), whereas the reference methods (WR and SWA) prospectively recorded dietary intake and PA for seven consecutive days. Thus, total time period covered by the test method and the reference methods ranged over about 2 months.

Seasonal variation of diet is an important factor to take into account due to changes in diet during a year. Collection of data from several seasons may decrease sampling

bias [109]. In the present validation study, visits at the study centre were distributed during all months during the years of 2014 and 2015, thereby including dietary intakes and physical activity from all seasons.

Different reporting of lifestyle factors have been documented among men and women [54, 55]. Therefore, we included both men and women in our validation study and stratified all analyses by sex (Paper II and Paper III).

CRC patients may experience altered memory, fatigue and breathlessness [110-112], which may hamper completion of extensive questionnaires. We therefore developed a short questionnaire (i.e. NORDIET-FFQ) specifically designed for the CRC-NORDIET study. The NORDIET-FFQ takes only about 15 minutes to complete, which may be more suitable for this group of patients in contrast to a long questionnaire taking about one hour to complete.

5.1.3 Subjects

The inclusion criteria chosen in the CRC-NORDIET study were based on general characteristics of the CRC patients in Norway; firstly, we included only patients with localised disease and a therefore a more favourable prognosis, relevant for the rationale of the study. These stage I-III patients constitute about two thirds of all CRC patients [113]. Secondly, according to the Cancer Registry of Norway the incidence of CRC increases from the age of 50 years both among men and women and the median age at CRC diagnosis is about 70 years old [113]. Thirdly, according to Statistics in Norway life expectancy for Norwegian men and women aged 80 years is nearly 90 years of age [114]. Hence, by including CRC patients with TNM stage I-III and aged between 50-80 years, the CRC-NORDIET study will recruit a representative sample of Norwegian CRC patients.

A sub-sample from the CRC-NORDIET study was invited to the validation study. At the time of the validation study (Paper I and Paper II) (Figure 2), all patients had completed primary treatment (i.e. mean time since last chemotherapy treatment was 155 days). Thus, we expected less variation in dietary intakes and PA due to treatment side-effects. As both study groups are equally exposed to data collection, including self-reporting of dietary intakes and PA, we expected equally learning effect in both groups. Therefore, all participants from both study groups were invited to the validation study. Moreover, with a response rate of about 92%, there was a high compliance and a minor selection bias in the study population (Paper II and Paper III).

5.2 Intervention in the CRC-NORDIET study

5.2.1 Dietary intervention

Although the risk factors for CRC are well documented [29, 59], no specific dietary recommendations exist for this group of patients. Therefore, health authorities in many countries give the same dietary recommendations to all cancer patients and follow the recommendation to the general population (Paper I, Paper II and Paper III). The Norwegian FBDG aim at preventing chronic diseases in the general population [59]. Given the fact that about 40% of CRC patients have at least one concomitant disease at diagnosis and are at increased risk of new primary chronic disease post-diagnosis, high compliance to the Norwegian FBDG post-diagnosis might reduce occurrences of comorbidities and co-mortalities and increase survival among this group of patients. The CRC-NORDIET study therefore aims to test the health effects of a prudent diet dampening inflammation and oxidative stress, like the Norwegian FBDG, in CRC patients (Paper I and Paper II).

Generally, in order to design the optimal intervention study focusing on behavioural change in lifestyle, it is important to take into account the specific needs among cancer patients. Timing of the intervention should coincide with the optimal time of motivation to undertake behavioural change. Previous studies have found this timing of the so called ‘teachable moment’ to be close to diagnosis [36, 45, 102], however this may vary depending on psychological stress, adjuvant therapy and rehabilitation regimes post-diagnosis [115]. Cancer patients suffer from side-effects of treatment that may require specific dietary needs. Dietary recommendations given in the CRC-NORDIET during the phase of recovery are individually adjusted according to these side-effects for patients in the dietary intervention group. After the phase of recovery, they are recommended to follow the Norwegian FBDG. In particular, increased intakes of fruit and vegetable, whole grains and fish, and reduced intakes of red and processed meat and foods rich in salt and sugar and no alcoholic drinks are

recommended. Moreover, maintaining a healthy weight and being moderate physical active for at least 150 minutes per week are also recommended. In addition, foods and drinks that have high contents of redox-active compounds, antioxidative effects and may have anti-inflammatory effects are recommended (Paper I). The participants in the control group receive similar information regarding the Norwegian FBDG as the general population (Paper I).

5.2.2 Intervention strategies

Interventions incorporating a behavioural theory, such as motivational interviewing or social cognitive theory have shown higher compliance to intervention strategies and may also reduce drop-out of intervention [45, 116, 117].

Other important factors for a successful intervention are to overcome barriers, such as the kind of intervention strategies and the timing of the strategies given during the intervention. Previous studies have reported different experiences with intervention strategies offered to older participants. Many of these intervention studies offer intensive individual counselling sessions performed by trained nutritionists [36, 50, 101, 117]. Ravasco *et al.* 2012 reported strong effect of early individualised nutritional counselling and education by a trained nutritionist during radiotherapy among CRC patients. They found improved nutritional status, improved quality of life and less toxicity due to radiotherapy in the group receiving individualised nutritional counselling compared to the two controls following usual care. This improved effects persisted after 3 months of intervention. Additionally, improved survival was documented in the intervention group at the long-term follow up of 6.5 years [50, 101]. As the face-to-face individual counselling is very resource demanding and may be a barrier for the participants due to travel distance, other studies have tested the effect of more resource effective strategies, such as home-based activities involving telephone counselling and mailed print outs [46, 118, 119]. The RENEW study [118]

found a significant improvement in functional decline among older overweight cancer patients (breast, prostate and CRC) receiving dietary and exercise intervention delivered by telephone counselling and mailed print material. Likewise, in the FRESH START study, they found a significant change in self-efficacy as a mediator of the effects of a mailed print intervention on the dietary, but not exercise, practices of newly diagnosed breast and prostate cancer patients [119].

Both RENEW and FRESH START studies were based on the Social Cognitive Theory [120]. Other studies have tested the effect of combining different intervention strategies among cancer patients. Campbell *et al.* 2009 [97] found a significant change in fruit and vegetable intake when combining tailoring print communication and motivational interviewing among older healthy adults, but not among CRC patients which could be explained by the long time since diagnosis and therefore less effect of motivation to behaviour change. Hence, timing and teachable moment might be important factors in motivation to change lifestyle behaviours.

Moreover, the WINS and WHEL studies investigated the effect of a combination of different intervention strategies in order to improve dietary intakes, such as intensive individual counselling, group sessions, cooking courses and tailored mailed prints, on disease free survival and overall survival among breast cancer patients [103, 121, 122]. Both studies resulted in increased intakes of fruits and vegetables and reduced dietary fat intakes, however, only WINS was able to show effects on survival [121, 122].

Motivational interviewing is used in the CRC-NORDIET study and the timing and intensity of the different intervention strategies were based on results from the abovementioned studies (Paper I). The heterogeneity among the patients in both study groups of the CRC-NORDIET study increases its complexity in achieving effects of intervention. However, this have been taken care of with the variety of

intervention strategies, involving both in-person individual dietary counselling, telephone dietary counselling, group sessions and a booklet with print outs, which may increase adherence to the dietary intervention. In particular, the intervention strategies offered in the CRC-NORDIET study were as follows (Paper I):

- Face-to-face individual dietary counselling
- Individual dietary counselling by phone-calls
- Group sessions such as a cooking course and an inspiration day (focusing on dietary intake and PA) at the study centre
- Incentives to make the healthy choice of food by a free-delivery of healthy foods
- Discount cards used for food shopping in supermarkets giving 25% discount on healthy foods (i.e. fresh fruits, berries and vegetables, fish and foods labelled with key-hole symbol)
- Web-page with food recipes and dietary recommendations
- Physical exercise in gym

The participants in the control group (group B) continued with their habitual diet. They also received invitation to an inspiration day at the study centre focusing on PA and physical exercise in gym. In addition, all participants in both groups receive reports from anthropometric measurements and some biological samplings performed during the visits at the study centre. Hence, all patients in both study groups are exposed to the same degree of intervention intensity and contact with the researchers when it comes to collection of data.

As mentioned above, duration of interventions aiming at behavioural changes should last for a certain time (i.e. 6-12 months) in order to cover the time needed for the changes to be accomplished [52, 102]. The long-term follow up period should continue with regular individual counselling to sustain maintenance of the behaviour

change. Otherwise, the changes have been shown to decrease with each year after intervention [52].

The 12-month duration of the intensive intervention in the CRC-NORDIET study was chosen due to the experiences from the other lifestyle intervention studies among cancer patients [52, 102], as behavioural changes takes time. Maintenance of the lifestyle changes in the long run after the end of the intervention depends on the intensity and kind of strategies offered during the maintenance period [52, 102, 123].

The 12-months intensive intervention in the CRC-NORDIET study is followed by a moderate intervention during a maintenance period lasting until 14 years of intervention. The dietary intervention group is offered individual dietary counselling by phone once a year and on the visits at the study centre, annual inspiration days, as well as continued access to the intervention web-page (Paper I). Hence, the moderate intervention during the maintenance period offered to the participants in the dietary intervention in the CRC-NORDIET study might help to sustain the dietary changes achieved during the intensive intervention period.

5.3 Endpoints and power calculations

In clinical trials, the research question should specify in detail the population and the endpoints of the study. In particular, defining survival outcomes is of great importance when designing a clinical trial. However, endpoints are inconsistently defined in most clinical trials, resulting in difficulties to compare studies. In order to improve this, a consensus report was published by Punt *et al.* [124]. They stated that disease-free survival (DFS) is the most frequently used endpoint in clinical cancer trials, as there are more events than in overall survival (OS), and hence allows for earlier measurement of intervention effects. However, definition of DFS varies in whether it includes 'second primary other cancer' as an event or not. Birgisson *et al.* [125] performed a study on the effect of including 'second primary other cancer' in

DFS among CRC patients. They found that 5-years DFS was 58% when including 'second primary other cancer' as an event and 62% when not.

5.3.1 Endpoints in the CRC-NORDIET-study

Primary endpoints

The two primary endpoints chosen in the CRC-NORDIET-study were DFS and OS, which will be assessed when all patients have completed 5, 10, and 15 years after baseline (Paper I). The DFS included second primary other cancer as an event in addition to local recurrence, or metastasis or death from any cause, according to the consensus report by Punt *et al*. 2007. OS was defined as death from any cause.

Secondary endpoints

In the CRC-NORDIET-study there are several secondary endpoints as shown in Paper I. Time to recurrence and the different survival endpoints will be assessed after 5, 10 and 15 years after baseline, whereas the other secondary endpoints not including survival will also be assessed after 6 months, 1 year and 3 years after baseline.

5.3.2 Endpoints in validation study

The primary endpoint of the validation study was to estimate adherence to the Norwegian FBDG and to assess the validity of the NORDIET-FFQ of dietary intakes and PA against the reference methods (WR and SWA, respectively) (Paper II and Paper III). Additionally, adherence to the recommendations of PA was also assessed by the HUNT-PAQ and evaluated against SWA.

5.3.3 Power calculations

In clinical trials involving survival endpoints, the time to an event is used as a measure of treatment effect. The length of time under study for each participants varies according to both time of enrolment to the study and time to event or missing data

(i.e. censoring) [126]. A common challenge in survival data is missing data due to censoring, in which the event did not occur before the end of the study. The reason for lack of registered events might be due to drop-out of the trial (i.e. withdrawal from the trial or emigration) or no events registered by the end of the trial [60].

The logrank test is commonly used for simple comparisons of survival curves and to test the effect of a covariate (i.e. study group), when the time-to-event data are censored and censoring is independent of prognosis and that there is an equal probability of survival for subjects recruited early and late to the study [127]. The corresponding test statistic is the hazard ratio (HR) [128-131]. The hazard is defined as the instantaneous incidence rate and the ratio of the rates in the two groups is the HR. A Cox model is often used when estimating effects of multiple covariates on the survival curves. Both logrank and Cox regression assumes proportional hazards. Moreover, intervention studies may suffer from high drop-outs leading to biased data. Survival analyses solve this by assuming similar hazard of the subjects who drop out as the subjects remaining in the study [128-131].

Power calculation in the CRC-NORDIET study

In the CRC-NORDIET study, the null hypothesis was equal survival distribution, i.e. a hazard ratio of 1, in both study groups at 5, 10 and 15 years after baseline. Estimation of sample sizes were calculated for OS and DFS assuming a Weibull distribution for survival times and censoring times in both study arms, a constant hazard ratio over time and a uniform drop-out of 2% of the participants per year (Paper I). It was also assumed that most of the participants who drop out still allow study investigators to follow up survival endpoints via national registries (based on written consent from the participants). The statistical method used to compute the sample size was the logrank test. The calculation of the sample size for a given hazard ratio was based on statistical power of 80% and significance level of 5% [126, 132, 133]. Data of the 5-year OS for CRC patients was taken from the Norwegian cancer registry annual report

[113], which in 2013 was 68% and was used as the expected OS for the control group in the study. In order to detect a 25% reduction in mortality in the intervention group, the required sample size was 250 in each study group to achieve a statistical power of 80%, corresponding to a HR of 0.71 after 5 years (Paper I). Likewise, a 25% reduction in events of DFS from 59% after 5 years of surgery [125] in the intervention group required 190 participants in each study group to achieve a power of 80% and resulting in a HR of 0.70 (Paper I). The intervention effect of 25% in reduction in mortality was based on literature consisting mainly of observational studies comparing high versus low adherence to a healthy diet and effects on survival from cancer, as this is the dominating study design within the research field of cancer and effects of diet [134-138].

Power calculation in the validation study

When comparing two methods measuring dietary intake and PA, the acceptable difference between the methods or the correlation coefficient can be used as test statistic in power calculations [139, 140]. Estimation of sample in the validation study was based on the detection of differences of 1 portion of fruit or vegetable (1 portion = 100 g) between test and reference method, assuming a standard deviation of 1.6 portion (or 160 g) with power of 80% and significance level of 5%. A sample size of 40 men and 40 women were needed to show this difference [141] (Paper II). Moreover, in order to detect a Pearson correlation coefficient of 0.5 or higher and with a significance level of 5 % and power of 80 %, about 38 men and 38 women was needed (Paper II and Paper III).

5.4 Statistical analysis

5.4.1 Statistical analysis in the CRC-NORDIET study

As the primary outcomes of the CRC-NORDIET-study are related to survival, Kaplan-Meier method will be used to estimate survival probabilities in order to compare estimated survival rates between the control and intervention groups at 5, 10, and 15 years follow-up [63]. When investigating the association between the survival time of the patients and prognostic and predictive biomarkers for survival, the Cox proportional hazards model will be used (Paper I). Different tests for two-group comparisons for the non-survival quantitative secondary endpoints will be performed either as parametric tests (for normally distributed variables) or non-parametric tests (for variables that are skewed or do not follow a normal distribution) to assess group differences at individual time-points. For binary and categorical secondary endpoints a chi-squared or Fisher's exact tests will be used to assess group differences. Evaluation of associations and changes in non-survival secondary endpoints over time and between the study groups will be analysed by mixed effect models and regression methods.

5.4.2 Statistical analysis in the validation study

To explore the validity of dietary and PA assessment methods, it is common to compare the test method with a reference method seen as superior to the test method [55]. The ability to estimate absolute values of dietary intakes or time in PA differs among the methods. If using a questionnaire as the test method, estimations of absolute intakes or time spent in an activity (expressed as mean or median) will only be valid on a group level due to the high variation in reporting among individuals. Commonly used estimate of variation of the mean is standard deviation (SD) whereas for median it is confidence intervals (CI), interquartile range (IQR) or percentiles. In the present validation study we used the median intakes and time

spent in PA with the variation presented as 5th and 95th percentile, as the distribution of residuals did not fulfil the assumption of normality.

Correlation

Another common method in assessing the validity of a questionnaire is to test the association related to ranking of individual`s dietary intake or time in PA, which are usually measured by the Pearson product-moment correlation coefficient assuming normal distribution or Spearman`s rho for non-normal distribution [54, 142]. The use of correlation coefficients in validation analyses have often been criticized, as it only reflects associations between methods and not the degree of agreement, resulting in reduced ability to detect systematic errors [142]. A poor agreement may exist even with a high correlation, which may be discovered by a significant difference between means or median between the methods [54]. Moreover, a high correlation may also hide measurement errors of clinical importance [142]. However, Pearson or Spearman correlation may be used if the aim of the validation is to evaluate the methods ability to rank individuals in the population studied. Overall, correlations as a measure of validity should be used with cautions and it requires other measures of agreement to reveal the degree of association between two methods. In the validation study, we used Spearman`s rho (non-normal distribution) in order to rank individual dietary intakes and PA (Paper II and Paper III).

Linear regression

Linear regression was used to reveal systematic over- or under reporting in the test-method in estimating PA (Paper III), with the reference-method as the independent variable and the difference between the test method and the reference-method as the dependent variable. If the slope of the regression line was significant different from zero it could indicate a systematic over- or under reporting [143].

Bland and Altman plot

Another method assessing the degree of agreement between two methods is plotting the differences against the mean of the two methods, called the Bland and Altman plot. Advantages of the Bland and Altman method is the use of mean and standard deviation of the differences between the two methods, as the standard deviation of the difference is not influenced by the between-person variation [55]. Moreover, as the data points are less compressed than in a regular scatter plot, it may be more likely to detect systematic bias. The Bland and Altman plot may reveal trends in data and systematic errors such as over- or underestimations or bias due to increase in difference between the methods with increased intakes. If the differences are normally distributed and there is no relation to the magnitude of the measures, the systematic error is estimated by the mean of the differences, while random error is estimated by the standard deviation (SD) of the differences. The limits of agreement are defined as mean ± 1.96 SD, indicating that there is a 95% probability of the difference between the methods for a random subject in the population to be within the limits of agreement. In the present validation study, we used Bland and Altman plot to measure the validity between the test methods and the reference methods (Paper II and Paper III).

Sensitivity and specificity analyses

As the aim of the NORDIET-FFQ was to estimate adherence to the Norwegian FBDG, we used sensitivity and specificity analyses to measure the questionnaires ability to identify individuals fulfilling or not fulfilling the guidelines. Sensitivity was defined as the percentage of subjects reported not fulfilling the recommendations for both the NORDIET-FFQ and WR/SWA assessments divided by the number of patients not fulfilling the recommendations according to the WR/SWA only. Specificity was defined as the percentage of subjects reporting to fulfil the recommendations for both the NORDIET-FFQ and WR/SWA assessments divided by the number of subjects

fulfilling the recommendations according to the WR/SWA only. Sensitivity and specificity above 60% was defined as good.

5.5 Adherence to guidelines

Generally, RCTs are designed to estimate effects of specific factors, such as nutrients or a single food [144]. However, since whole foods and dietary patterns, and not only a few nutrients, have been associated with risk of chronic diseases [1, 29, 34], RCTs investigating effects of the whole-food approach will broaden the knowledge about the efficacy and causal inference of the dietary intervention on the disease related outcomes. Moreover, in order to obtain statistical power of effect on dietary change on the outcome, a high compliance to the dietary intervention is of crucial importance.

In the CRC-NORDIET study, the NORDIET-FFQ was designed to estimate adherence to the main guidelines of the Norwegian FBDG. Since the intention also was to design a short FFQ, questions needed to estimate a whole diet in order to calculate energy and nutrient intakes, and consequently many more questions, were therefore not included. The dietary guidelines estimated from the NORDIET-FFQ are described in Paper II and Paper III. Limits of dietary intakes and PA required to fulfil Norwegian FBDG are defined in Paper II and Paper III. These limits were used in the recoding into new dichotomous variables to calculate adherence to the guidelines (i.e. sensitivity and specificity analyses).

5.5.1 Dietary recommendations

The NORDIET-FFQ (Supplementary file 1) asked for food items which were ready to eat and frequency and portions sizes are further defined in Table 3. Calculation of limits of intakes for certain food groups which were not specified in detail in Paper II will be emphasised in the following sections below.

Whole grain products

To be able to estimate intake of whole grains, we made a whole grain factor used to calculate the whole grain content in the whole grain products. The calculation was based on the assumption that bread consists of 60% flour (ready to eat). In Norway, commercially produced bread may be labelled with a general symbol for 4 different ranges of whole grain flour content; 0-24%, 25-49%, 50-74% and 75-100%. We used the lower range of the whole grain scale [145] in the calculations (Paper II). For instance, if the content of whole grain in bread was 75-100% the whole grain factor was calculated as follows: (60*75)/10000=0.45. To estimate whole grain intake the whole grain factor of 0.45 was then multiplied with grams per day of reported intakes of bread with 75-100% whole grain flour. Moreover, it was assumed that boiled rice and pasta contains 70% water and 30% cereals [59], hence the whole grain factor for brown rice and whole grain pasta was 0.3.

Nuts

In Paper II we calculated separate limits for fulfilling recommendation of nut intake for normal-weight and overweight (i.e. BMI < 25 or BMI ≥ 25, respectively), with an upper limit for overweight of 30 g/d, but no limit for normal-weight. This was based on the recommendation of maintaining a healthy weight in the Norwegian FBDG, and the assumption that high nut intake may contribute with excessive energy intake leading to weight gain. However, there is inconsistent evidence in the literature of the association between high nut intakes and weight gain [146, 147]. Freisling and co-workers showed an association with reduced weight gain among those with highest intakes of nuts in a sub-population of the EPIC cohort (EPIC-PANACEA cohort) [148]. Therefore, in the present PhD thesis adjustment of the definition of recommendation of unsalted nuts to daily intake of at least 20g/d or more, without any restriction on BMI, was made. There were only small changes in sensitivity and specificity, from 93% to 91.5% and 55.6% to 60%, respectively. Thus, the NORDIET-FFQ was able to

identify individuals both fulfilling and not fulfilling the recommendation of nut intake of at least 20 g/d.

5.5.2 Translation of qualitative recommendations into quantitative values

In order to measure adherence to the qualitative recommendations of the Norwegian FBDG we had to translate these qualitative recommendations to quantitative values and lower limits of intake.

Oils, butter and margarine

The question regarding intakes of dietary fats, such as oil, butter and margarine was qualitative and asked for what kind of fat the subjects usually use in cooking and as spread, respectively. Both categories were given a value in order to calculate correlation between the methods and compliance to the recommendations. Values for each response were as follows:

No intake was given zero points, preference to use soft margarine or preference to use oils were given 2 points, preference to use butter was given 0.5 point. The sum of the two items within this category was calculated, of which the value of 2 and 4 indicated mostly healthy margarine and oil, value 2.5 indicated use of oils, margarine and butter, whereas values 0.5 and 1 indicated use of only butter. Moreover, in order to calculate adherence to the guidelines, these values were categorized into a dichotomous variable (0 or 1). The values of 2 and 4 were recoded into 1 (i.e. fulfilling guideline), whereas the vales of 2.5, 1, 0.5 and 0 were recoded into 0 (i.e. not fulfilling guideline).

5.5.3 Physical activity recommendations

The PA recommendation was defined as moderate-to-vigorous intensity PA (MVPA): MPA + (VPA*2) [149]. The cut-off points for fulfilling recommendations of MPA and MVPA were at least 150 minutes per week, whereas it was at least 75 minutes per week for VPA. The activities should be in bouts of 10 and more consecutive minutes.

Participants who reported to fulfil the MVPA of at least 150 minutes per week were 66% with the NORDIET-FFQ and 55% with the SWA (Paper III). The over-reporting of meeting the PA recommendations has also been shown in cancer patients by Vassbakk- Brovold and co-workers [91].

Table 3: Overview of portions sizes, amounts, whole grain factor and scores of food intake and physical activity used in the NORDIET- FFQ. Frequencies are described in footnotes.

Questions	
Question 2: Fruits and berries*	**Amount**
Large fruit	1 piece =100g
Medium fruit	1 piece =50g
Small fruit	1 piece =10g
Berries	1 dl = 55
Dried fruit	1 dl = 60
Question 3: Nuts*	**Portion size**
Unsalted nuts	1 portion = 25
Salted nuts	1 portion = 25
Question 4: Vegetables*	**Amount**
Garlic (fresh)	1 slice = 3g
Onion, leek, scallions	1 ss = 10g
Tomato	1 piece= 65g
Tomato sauce	1 dl = 100g
Mixed salad	Small bowl = 100g
Other vegetables	1 dl = 60g
Question 5: Cereals*	**Amount**
Cereals with added sugar	1 dl = 50g
Cereals without added sugar	1 dl = 50g
Question 6: Drinks*	**Amount**
Water	1 glass = 200g
Other drinks without added sugar	1 glass = 200g
Fruit juice without added sugar	1 glass = 200g
Other drinks with added sugar	1 glass = 200g
Milk	1 glass = 200g
Beer with alcohol	1 glass= 500
Vine with alcohol	1 glass = 110
Spirit	1 glass = 40
Coffee	1 cup= 250
Tee	1 cup= 300
Question 7: Cakes, dessert, candy*	**Amount**
Cakes, sweet bakery products, waffles, biscuit	1 slice = 60g
Dessert	1 dl = 90g
Chocolate, candy	1 hg = 100g
Chips	1 dl = 15g
Question 8: Bread**	**Amount**
White bread: 0-25% whole grains flour	1 slice= 30g
Bread made from 25-50% whole grains flour	1 slice= 36g
Bread made from 50-75% whole grains flour	1 slice= 60g
Bread made from 75-100% whole grains flour	1 slice= 60g
White crispbread	1 slice= 12g
Whole grain crispbread	1 slice= 14g
Whole grains in products	**Whole grain factor**
White bread: 0-25% whole grains flour	0
Bread made from 25-50% whole grains flour	0.15
Bread made from 50-75% whole grains flour	0.30
Bread made from 75-100% whole grains flour	0.45
White crispbread	0
Whole grain crispbread	1
Cereals with added sugar	0.25
Cereals without added sugar	0.75

Whole grain pasta	0.3
Brown rice	0.3
Question 9: Spreads on bread* **	**Amount**
Cheese with high fat content	1 slice = 10g
Cheese with low fat content	1 slice = 10g
Fish	1 portion =36g
Red meat	1 slice = 10g
White meat	1 slice = 10g
Spreads with added sugar	1 portion =20g
Vegetable and fruit as spreads	1 portion =15g
Question 10: Margarine, butter and oils	**Score**
Cooking, bakery	Do not use = 0
Spreads on bread/rolls	Mainly use soft margarines=2 Mainly use hard margarines =0.5 Mainly use oils = 2
Question 11: Dairy products*	**Amount**
Dairy products with high fat content	1 dl= 100g
Dairy products with low fat content	1 dl= 100g
Question 12: Fish for dinner*	**Portion size**
Fatty fish	1 portion = 145 g
Lean fish	1 portion = 145 g
Processed fish	1 portion = 180 g
Question 13: Meat for dinner*	**Portion size**
Red meat	1 portion = 150 g
Processed red meat	1 portion = 150 g
White meat	1 portion = 150 g
Processed white meat	1 portion = 150 g
Question 14: Rice and pasta*	**Amount**
White rice	1 dl= 80g
Brown rice	1 dl= 80g
Refined pasta	1 dl= 125g
Whole grain pasta	1 dl= 125g
Question 15: Dietary supplements*	**Amount**
Cod liver oil	1 ts=5g, 1bs=7, 1 ss=11g
Cod liver oil/fish oils in capsules	1 capsule=1
Vitamin D	1 capsule = 1
Multivitamin tablets	1 tablet = 1
Question 16: Physical activity*	**Time in physical activity**
Moderate intensity	3-6 METS
High intensity	6-9 METS
	Minutes in calculation for both categories of intensity: 1-4=2, 5-9=7, 10-15=12.5, 16-20=18, 21-30=25.5, 31-45=38, 46-60=53, 60+=72

*Frequency: 0=0, 1=0.14, 2=0.29, 3=0.43, 4=0.57, 5=0.71, 6-7 =0.93, 8+ =1.37

**Frequency: 0=0, ½=0.5, 1=1, 2=2, 3=3, 4=4, 5=5, 6=6, 7=7, 8=8, 9=9, 10=10, 11=11, 12=14.4

*** Frequency: 0=0, 1=1, 2-3=2.5, 4-5=4.5, 6-7=6.5, 8-12=10, 13-18=15.5, 19-24=21.5, 25-30=27.5, 31+ =37.2

5.6 Diet and physical activity assessments in clinical studies

In order to measure compliance to a dietary intervention, it is important to validate the dietary assessment tool in a sub-sample of the study population [55]. More knowledge on how to interpret the results can then be made when measuring associations with the outcome of the study, such as disease free survival and overall survival.

There was a need for a short FFQ estimating adherence to the Norwegian FBDG in recent weeks (i.e. 1-2 months) to identify dietary changes of these behaviours in CRC patients [89, 93, 150-152] and to measure compliance to the dietary intervention. Therefore, the short NORDIET-FFQ was designed and validated in the CRC-NORDIET study and contained 63 food items and 2 items of PA (Supplementary file 1, Paper II and Paper III). The review of Cade *et al*. 2002 [68] documented the medium size of short FFQs to be 79 food items, ranging from 5-350 food items. Interestingly, the study of Willett *et al.* 2013 [55] compared a 44-item FFQ with a 273-item FFQ and concluded a rapidly decreasing marginal gain in information with increase in number of food items included. We therefore expected valid estimates of dietary intakes with the short NORDIET-FFQ in the present validation study.

5.6.1 Assessment of diet

When designing a FFQ, the purpose of the FFQ, i.e. what part of the diet the FFQ is intended to measure, will have an impact on what type of questions and food items to include [55, 68]. If the purpose of the FFQ is to measure only certain food items or food groups, a comprehensive food list covering all foods may be unnecessary [68]. Moreover, choosing single or grouped food items in the FFQ is also necessary to consider. In that case, one should be aware, that single food items can be aggregated into food groups, but food groups cannot be separated [68]. Generally, several single food items tend to result in overestimation, whereas food groups often results in

underestimation of intakes of the food group in focus [54, 55, 68]. In the present validation study, the over-reporting of whole grain products in total measured by the NORDIET-FFQ might be explained by the reporting of several single whole grain food items, such as bread, pasta, rice and cereals.

Depending on the aim of the questionnaire, some grouping of foods are necessary, but it should be based on *a priori* hypothesis [68]. In the CRC-NORDIET study, the questions in the NORDIET-FFQ corresponded to the food groups relevant for the Norwegian FBDG, and therefore several food items were aggregated into food groups with adjusted portion sizes accordingly. For instance, the different items of fruits were grouped into three different levels of sizes, i.e. large, medium and small (Supplementary file 1). The group of large fruit included apple (100g), nectarine (100g) oranges (200g), banana (110g), and one slice of melon (65g), which resulted in an overall portion size of 100g (Table 3). Medium fruits (i.e. clementine, kiwi and plums) were assigned a portion size of 50g and small fruits (i.e. grapes) were assigned a portion size of 10g. Total fruit intake was calculated by the sum of these three levels of fruits, in addition to dried fruits, berries, one glass of juice (=100g) and fruits used as spread (divided by two, since the same question also asked for vegetables) and then multiplied by the frequency per day (Table 3, Supplementary file 1). Generally, it is recommended to use multiple, simple and clear questions rather than complex and combined questions when designing an FFQ [55, 92, 153-155]. However, we ended up with choosing combined questions grouped according to the size of the fruit, which might help the respondents to visualise the amount of fruit intake.

Single food items which were not detailed described in detail in Paper II will be emphasised in the following sections below.

Fruit and vegetables

Results from the validation analyses were acceptable, shown by fair and satisfactory correlations of the single items of fruit (sum of large, medium, small fruit and fruit as spread), berries, dried fruit and juice, as well as for the combination of fruits (sum of fruits, berries, dried fruit and juice) (Paper II, Supplementary file 1). Moreover, median intakes of fruits in similar abovementioned combinations did not differ significantly between the methods (e.g. the NORDIET-FFQ and WR), except for dried fruit.

Bland and Altman plots for most of the single items of fruits as well as the whole group of 'Fruit and berries', showed a small mean difference (i.e. small systematic error), with wide but evenly distribution of the differences above and below the mean difference (i.e. high random error). Interpretation of the limits of agreement indicated a 95% probability to estimate individual differences in intakes of 'Fruit and berries' within the range of error of 250 g/d.

The questions regarding vegetables in the NORDIET-FFQ followed the specific recommendations as described in the Norwegian FBDG [59], including some single food items and some combinations of several vegetables (Supplementary file 1). It turned out that it was more challenging for the subjects to interpret intakes of vegetable in the combined groups than in the questions with single vegetable item. For instance, there was a fair correlation between the two methods for garlic (not men), onion, tomato and tomato sauce (only men), whereas poor correlation for the combined group of 'mixed salad' and 'other vegetables' (except for women which showed fair correlations for both groups) (Paper II). However, onion (only women), tomato sauce (only men), 'mixed salad' and 'other vegetables' (only women) were the only groups of vegetables which did not differ significantly in median intakes between the methods. When all single items of vegetables were combined into one group, the correlation become poor but there was no significant differences in

median intakes between the two methods on group level. The Bland and Altman plots for most of the single items as well as for the whole group of 'Vegetables' showed small mean differences (i.e. small systematic error) but with increasing differences with higher intakes (i.e. high random error).

Fish

Intakes of fish was covered by four single questions about on fatty fish (e.g. salmon, trout, herring, halibut), lean fish (e.g. cod, pollock, angler), processed fish (e.g. fish gratin, fish cakes) and fish as spread (e.g. mackerel, smoked salmon, herring). The four questions were combined into one main group of fish. The NORDIET-FFQ was able to rank individual intakes of all these items, except for intakes of total fish and fatty fish (including fish as spread) among women. Estimation of median intakes was good for total fish, fatty fish (only men), lean fish and processed fish. There was a small mean difference and limits of agreements within one portion of fish.

Nuts

Some questions were found valid both as single item questions and when grouped together. Salted and unsalted nuts represented the two single items which were combined to the main group of nuts. The NORDIET-FFQ was able to rank individual intakes of unsalted nuts, salted nuts (only women) and the combined group of nuts, and to estimate intake of unsalted nuts (only men), salted nuts (only women) and the combined group of nuts (only women).

Dairy products

As for the other food groups, also dairy products consisted of several single items in the NORDIET-FFQ, which were put together into different groups in order to estimate the recommendations of dairy products. For instance, the two main groups of 'high fat dairy products' and 'low fat dairy products' consisted of single food items of high or low fat cheese, milk and dairy products, respectively. The NORDIET-FFQ was able

to estimate median intakes and to rank individual intakes (not men) of 'high fat dairy products', whereas it was only able to rank individual intakes of 'low fat dairy products'. Almost all single items of dairy products (e.g. milk, cheese, low fat dairy (only men), high fat dairy (only women)) showed fair or satisfactory correlations, except for low and high fat dairy products in total.

Measurement errors

We observed both under- and overestimation of different food groups, which may be explained by the existence of random errors between the individuals. As random errors between the methods seldom are related, the possible related errors between methods may be associated with the food composition database (i.e. systematic errors). The NORDIET-FFQ was closed-ended which depends on memory and conceptualism of portion sizes, whereas the reference method was open-ended without these dependencies. The portion sizes used in the NORDIET-FFQ was based on the food composition database and nutrient calculation system developed at the Department of Nutrition, University of Oslo (KBS, version 4.7, 2010, AE-10) (Table 3). The same food database was used when coding all foods reported in the WR. Hence, systematic errors could be explained by the portion sizes in the shared food database, which have also been documented by other studies [87, 89, 156-159].

Missing values

The manual coding and import of data from the WR were done by two trained researchers, in accordance with a protocol developed at the Department of Nutrition, University of Oslo. In cases when food items reported in the WR were not included in the food database, the most similar food item when it comes to content of energy and nutrients were used. Similarly, when there was limited information about a food item in the WR, such as only a slice of bread without any specification of the degree of whole grain content, it was coded as the standard type of bread with medium content of whole grain into the food database. Likewise, if portion size was lacking, a

standard portion size for that particular food item was used. This could also have contributed to the under- or over reporting of the actual intake. In the NOWAC study imputation of missing consumption frequencies with null value (i.e. no consumption) and missing portions sizes with smallest amount were used, which resulted in a conservative estimation or under-reporting of intakes for these food items [160].

Similar rules were used in correction of missing responses in the NORDIET-FFQ (Paper II) which may partly have contributed to the under-reporting observed for some food groups.

Moreover, the standard portion size for meat and fish for dinner used in the questionnaire were defined by the food database (KBS), which might have been different from the intakes recorded in the WR by the participants. These standard definitions could thereby have contributed to some of the observed systematic error for these food groups.

Results from validation of dietary intakes

Overall, the NORDIET-FFQ showed good ability in estimating intakes of plant-based foods, fish, dairy products, meat and energy-dense foods, adequate ranking of individuals according to intake of most recommendations except for processed meat, non-processed meat and vegetables and importantly a good ability in identifying those patients in need for dietary counselling for the foods which are known to modulate the risk CRC (Paper II). The food groups estimated by the NORDIET-FFQ are comparable with other similar studies [89, 90, 141, 156]. In particular, intakes of fruits, vegetables and fish estimated by the NORDIET-FFQ was comparable with the Norwegian national-wide survey, NORKOST 3 [141]. Moreover, Carlsen and co-workers found Spearman's correlation rho ranging from 0.31 to 0.70 for intakes of fruit, fruit and vegetables, nuts and alcoholic drinks between a long FFQ and WR, which also is comparable with the present study [156]. Welch and co-workers documented lower intakes of total and fatty fish intakes measured by both 7-day WR

and FFQ among individuals from the EIPC-Norfolk population compared to the present study [161]. Intakes of whole grain products in the Danish Diet, Cancer and Health cohort were estimated by a long FFQ and showed higher intakes than the CRC patients in the present study [162]. Thus, results from the NORDIET-FFQ are comparable with findings from other studies. However, precaution should be made when comparing results from different studies, due to different use of assessment methods, definitions of food items and portion size as well as different populations.

5.6.2 Assessment of physical activity

NORDIET-FFQ

The NORDIET-FFQ aimed at estimating PA according to the Norwegian FBDG, therefore the two items on PA focused solely on MPA and VPA intensities (Supplementary file 1, Paper III). MPA was described as activities similar to brisk walking, household chores or other activities resulting in slight breathlessness, whereas VPA was exemplified by running, cross-country skiing or other activities resulting in high breathlessness (Paper III). The responses of frequencies were given in times per week (time divided by seven) and the responses of duration in minutes coded as described in Table 3. Additionally, categories of 10-minutes bouts were computed and defined as ten or more consecutive minutes within each intensity level. This resulted in data on 10-minutes bouts of MPA, VPA and MVPA, as defined by the recommendations. The lower range of responses for durations of 2 or 7 minutes allowed the participant to report shorter time of activity than the recommended 10-minutes bout. Similar rules for imputation of missing values were used as for the food items. Self-reported time in MVPA estimated by the short form International Physical Activity Questionnaire (IPAQ-sf) was greatly over-reported by cancer patients in the study of Vassbakk-Brovold and co-workers as compared to SWA, and also as compared to the NORDIET-FFQ in the present study (Paper III) [91]. Ekelund and co-workers documented less time in MPA estimated by IPAQ-sf among

healthy Swedish individuals compared to the result form the NORDIET-FFQ [163]. Hence, it is important to be aware of the strength and limitations among the different PA assessment methods used in different populations.

HUNT-PAQ

The participants in the CRC-NORDIET study also completed a PA questionnaire, HUNT-PAQ, which was based on the PA questionnaire, HUNT 3, used in the large health survey in Nord-Trøndelag county in Norway (Supplementary file 2) [76, 77]. The response alternatives were different from the responses in the NORDIET-FFQ, with regard to intensity, duration and frequency. The single question on level of intensity (e.g. low, moderate or vigorous) restricted the participant to choose only one of them, which might explain the higher degree of under-reporting of PA as compared to the NORDIET-FFQ (Paper III) where it is possible to choose more than one alternative of intensity. Moreover, the lowest duration of activity was 12 minutes, with no opportunity to report shorter time of activities as is possible in the NORDIET-FFQ. Since both activity levels, MPA and VPA, were reported from 12 minutes and higher in the HUNT-PAQ, these were equally defined as the 10-minutes bouts in the NORDIET-FFQ. Moreover, the HUNT-PAQ contained one numeric question on sedentary time reported in hours per day. This was not included in the NORDIET-FFQ.

Reporting bias

Generally, bias in reporting of activity intensity seems to be influenced by the number of questions for a specific activity within a questionnaire [54, 55]. Both questionnaires in the validation study contained only a few single questions on PA. The self-reported sedentary time in the present study was based on one single-item question and was greatly under-reported by the HUNT-PAQ compared to SWA, which are supported by other studies [164, 165]. Moreover, in a study of cancer survivors undergoing chemotherapy, PA was self-reported by the short form International PA

Questionnaire (IPAQ-sf) [91], which greatly over-reported PA with 366% compared to the objective sensor, SWA. The IPAQ-sf contained nine questions on PA [84], whereas the NORDIET-FFQ and HUNT-PAQ contained two and four questions on PA, respectively. Thus, the numbers of questions within the intensity of activities influences degree of under- or over-reporting.

Defining intensity of PA

In order to compare the different physical activity categories reported by the questionnaires in the validation study with the reference method (SWA), MPA and VPA were defined as 3-6 and >6 METs, respectively [149, 166] (Paper III). Moreover, sedentary time was defined as all daily activities ≤1.5 METs, of which night-time sleep was removed (a priori defined as from 12 midnight to 6.00 a.m.). Night-time was removed in order to conform to the question about sedentary time during day-time in the HUNT-PAQ. In cancer patients, this definition may be challenged by several disease- and treatment side-effects influencing sleeping pattern due to increased need of resting time [167]. Higher precision in reporting daily sedentary time would have been reached with a diary report completed by each patient specifying time of night.

All activities were calculated and expressed in minutes or hours per week (sedentary time). MPA and VPA reported and estimated by the questionnaires and SWA were grouped into a new variable reflecting the recommendation of PA, called moderate-to-vigorous PA (MVPA= MPA + (VPA*2)) (Paper III). Vigorous intensity was weighed twice as much as the moderate intensity due to the definition of the recommendation [59, 149, 166].

Results from validation of PA

Results from the validation analyses showed that the NORDIET-FFQ was able to estimate time in MVPA and MPA (only women) on group level, but not time in VPA.

However, all intensities were significantly under-reported by the HUNT-PAQ on group level. Both questionnaires were poor in ranking individual time in MVPA, MPA and VPA, except for a fair Spearman`s rho with the HUNT-PAQ for MPA and sedentary time among women only. The Bland and Altman plot revealed a smaller percent mean difference with the NORDIET-FFQ than the HUNT-PAQ as compared to the SWA, indicating an increased accuracy in reporting of intensities with the NORDIET-FFQ compared to the HUNT-PAQ.

Moreover, linear regression revealed increased under-reporting of higher amounts of PA in both questionnaires, indicating a systematic bias. However, the Bland and Altman plot showed evenly distributed differences above and below the mean difference which indicated no systematic bias of activities in any of the questionnaires. When looking at the distribution of differences in the Bland and Altman plots, the systematic bias estimated by the linear regression seem to be due for intensities higher than 250 and 200 min/week with the NORDIET-FFQ and HUNT-PAQ, respectively. Linear regression includes all data plots into the estimation of association between two methods, and is not able to differentiate association according to the distribution of the differences.

Hence, the NORDIET-FFQ was able to measure intensities up to about 250 min/week on group level, but the HUNT-PAQ was less well suited to measure the corresponding intensities (Paper III). Moreover, objective monitors have been shown to give more accurate measurements of intensity-specific physical activities than self-reported activities from questionnaires [168]. In particular, accurate measurement of sedentary time is of great importance when investigating effects on survival among cancer patients. Therefore, sedentary time measured by the SWA in the validation study is preferable to use as opposed to self-reported sedentary time from the HUNT-PAQ.

5.7 External validity

Internal validity refers to which degree the results obtained is representative for the subjects in the study, whereas external validity refers to how the information relates to the source population from which the study sample is drawn [54, 60, 62]. External validity depends on a good internal validity, but a study sample with good internal validity might not be representative segment of the source population, thereby violating the possibility of generalisation of the results outside the study cohort [54]. There are several factors which may cause biased effect estimates in intervention studies which are related to the design and implementation of the study [60]. Internal validity refers to no bias due to the conduction of the study, the analyses of data and the interpretation of the results. Even if the study cohort is not representative of the general population in a RCT, it might have external validity (i.e. generalizable) due to the intervention effect on the process which is investigated [60].

CRC-NORDIET study

All CRC patients undergoing surgery at Oslo University Hospitals and Akershus University Hospital within the South-Eastern Norway Health Authority (Paper I) and fulfilling the inclusion criteria of the CRC-NORDIET study (Paper I) are invited to the study. Since the two hospitals covers a population of about 900 000 and the vast majority of the CRC surgery for this population is performed at these two hospitals [169], this population can be seen as representative for all CRC patients in Norway. Moreover, preliminary estimation shows a participation rate of about 50 percent (data not shown) to the CRC-NORDIET study. This might be explained by the challenges of recruitment close to surgery, as the patients are faced with altered health due to treatment effects. Another barrier may be the travel distance to the

study centre. To overcome some of these barriers, we offered several incentives such as travel cost reimbursement, individual feedback on diet, anthropometric and biological measurements performed at the study centre. Moreover, the proportions of colon and rectum cancer, men and women, TNM stages (I-III) and age groups in the CRC-NORDIET study population (preliminary data not shown), seem to follow similar proportions as in the general population of CRC patients in Norway [32]. Thus, the CRC-NORDIET study population may be representative (i.e. external valid) for all CRC patients with primary invasive CRC, TNM stages I-III and ages between 50-80 years old. Results from the CRC-NORDIET study might therefore be incorporated into the clinical care for all CRC patients in Norway with similar characteristics.

Validation study

Generally, the representativeness of subjects is less important in a validation study, because the participants act as their own controls. However, selection bias may alter the external validity by including participants which are most conscious about their dietary consumption leading to increased precision in reporting of dietary intakes with the two dietary assessment methods included in the validation study. There was a higher proportion of participants with high education in the validation study (51%) as compared to the general Norwegian population (33%) [114]. This may have influenced the precision in reporting of dietary intakes (i.e. improved precision) in both methods. Mean age of the participations in the validation study is similar as the mean age of all CRC patients in Norway.

As abovementioned, the high participant rate of 92% to the validation study (Paper II and Paper III) indicates good external validity (i.e. no selection bias) as the participants may be representative for the study population included in the CRC-NORDIET study. This is also reflected by the almost equal proportions of colon and rectum cancer, TNM stages, sex and ages (Paper II and Paper III) as both the study

population of CRC-NORDIET study (preliminary results not shown) and the general CRC population in Norway [32].

Importantly, generalization of data from the validation study to other populations than Norwegian CRC patients must be interpreted with precautions because other populations may be different from the population included in the validation study [55]. However, as the NORDIET-FFQ and the HUNT-PAQ are validated in a population of CRC patients, the questionnaires might give valid estimates of dietary intakes and PA according to the Norwegian FBDG in other chronical diseased patients facing similar symptoms of attenuated health.

6 Conclusions

6.1 The CRC-NORDIET study

The design of the CRC-NORDIET study is unique in several aspects related to the interventions as well as outcomes, such as:

- ✓ The RCT design enables equal distribution of confounding factors in both study groups.
- ✓ The control group is following usual care when it comes to dietary recommendations and receives similar intervention and recording of PA as the dietary intervention group.
- ✓ There are two primary survival endpoints and several secondary endpoints focusing on both survival and non-survival endpoints. The first primary endpoint is DFS which include 'second primary other cancer' as an event in addition to local recurrence, or metastasis or death from any cause. The second primary endpoint is OS which includes death from any cause. Power calculations have been performed on these endpoints after 5, 10 and 15 years of baseline.
- ✓ The study is designed with a long (i.e. 12 months) and intensive dietary intervention with subsequent moderate maintenance during a long-term following up period of 15 years. This may ensure long enough time both to accomplish changes in dietary habits and also to measure effects of these changes on the endpoints of the study.
- ✓ The intervention consists of several strategies given both as individual and group sessions, individual counselling offered both as face-to face and home-based and economic incentives such as free food delivery and discount card in grocery stores. These different intervention strategies may fulfil the certain

needs in order to change dietary habits among the patients and thus contribute to a higher overall compliance to the dietary intervention.

- ✓ Recording dietary intakes several times during the study at all 9 visits will ensure increased knowledge regarding dietary changes during the study. These changes may have important impact on the health related outcomes in the study; thus it is of great importance to measure these changes.

Overall, the results from the CRC-NORDIET study will contribute with valuable knowledge about the effects of a healthy diet on survival endpoints as well as on the burden of the treatment effects frequently found among CRC survivors. Additionally, the CRC-NORDIET study is unique in its broad and thorough characterising of the changes in nutritional status, anthropometric measurements, body composition, physical functioning, dietary intakes, disease related factors and quality of life during the period with long term following-up post-surgery.

6.2 Validation study

The aim of the NORDIET-FFQ was to estimate adherence to the Norwegian FBDG. Moreover, it was also important that it should be short and easy to complete for the respondents, as well as less burdensome data handling for the researchers as compared to larger questionnaires. In addition, the subjects in the CRC-NORDIET study were asked to complete a questionnaire on PA and sedentary time (i.e. HUNT-PAQ). The HUNT-PAQ is adapted from the questionnaire used in the HUNT-1 study (The Nord-Trøndelag Health Study), which has been used to report PA and sedentary time in a general healthy population in Nord-Trøndelag County in Norway. Since this was the first time the HUNT-PAQ was used in a cancer population, we needed to test the validity of the questionnaire in the CRC-NORDIET population.

Results from the validation study can be concluded as follows:

Dietary intakes:

- ✓ The NORDIET-FFQ was able on group level to estimate intakes of most food groups related to the Norwegian FBDG, such as fruits, vegetables, nuts, fish, dairy products, meat, beverages and sugar- and fat rich foods.
- ✓ The NORDIET-FFQ was able to rank individual intakes, such as fruits, fruit and vegetables, whole grains, red meat, alcoholic beverages and dairy products. The NORDIET-FFQ was not able to rank individual intakes of processed meat, non-processed meat and vegetables.
- ✓ The NORDIET-FFQ was able to identify those individuals in need for dietary counselling for the foods which are shown to be associated with risk of CRC, such as fruits and vegetables, fruits, vegetables, unsalted nuts, whole grain products, low fat dairy products, processed meat, water, alcoholic beverages and sugar- and fat rich foods.

PA:

- ✓ The NORDIET-FFQ was able to estimate time in MVPA and MPA (only women) on group level, but not time in VPA.
- ✓ The NORDIET-FFQ showed limited ability to rank individuals according to time in different PA intensities.
- ✓ The NORDIET-FFQ was able to identify those fulfilling the PA recommendations, but not those in need of PA counselling.
- ✓ The HUNT-PAQ significantly under-reported all PA intensities and sedentary time on group level.
- ✓ The HUNT-PAQ was able to rank individuals according to MPA and sedentary time among women only.
- ✓ The HUNT-PAQ was able to identify individuals in need of PA counselling.

Overall, the NORDIET-FFQ gives valid estimates of adherence to Norwegian FBDG and was able to identify those individuals in need for dietary counselling for the foods which are shown to be associated with risk of CRC. Moreover, the NORDIET-FFQ gives valid estimates of time in MVPA and MPA (only women) on group level and was able to identify those individuals fulfilling the recommendations of PA. The HUNT-PAQ was able to rank individual time in MPA and sedentary time among women and to identify individuals in need of PA counselling. However, objective monitor should be considered used when more accurate individual data on PA and sedentary time is needed.

7 Future perspectives

To our knowledge, the CRC-NORDIET study is the first of its kind among CRC patients (Paper I). The huge amount of data sampled during this long term clinical study, will generate several future sub-studies focusing on many central aspects of crucial importance for the prognosis among CRC survivors.

The NORDIET-FFQ developed and validated in the present validation study (Paper II and Paper III), will contribute with valuable information regarding dietary intakes and adherence to the Norwegian FBDG which may have significant impact on several outcomes in the CRC-NORDIET study.

We are planning to translate the NORDIET-FFQ into a web-based questionnaire. This may be advantageous for the respondents due to the greater opportunity of getting informative text and pictures of portions sizes of foods, which may improve the precision when reporting dietary intakes. Moreover, web-based questionnaires are advantageous due to more efficient data handling and thus also more economically advantageous for the study. However, a new validation of the web-based NORDIET-FFQ must then be considered as estimates of dietary intakes and time in physical activity may be differently from the paper-based version. Additionally, in order to determine if the results from the NORDEIT-FFQ are reproducible, a reproducibility test (i.e. test-retest) has to be performed.

Several different healthy indices can be made based on the cut-off values of the Norwegian FBDG defined and evaluated in the present validation study. These future healthy indices may improve estimations of adherence to Norwegian FBDG in other intervention studies as well as in health care practice performing individual dietary counselling among cancer patients.

Since the CRC-NORDIET study is an ongoing trial and still recruiting participants, we have not analysed biomarkers for dietary intakes. These analyses will be performed when all 500 participants in the CRC-NORDIET study have completed the baseline visit. Biomarkers give valuable data on intakes for certain foods, which can be used as a reference method in validation of the web-based NORDIET-FFQ and also as explanatory factors in other future sub-studies from the CRC-NORDIET study.

The results from the CRC-NORDIET study on survival among CRC patients will contribute with valuable knowledge, which may be used as evidence in the future guidelines for CRC survivors. However, results from other studies are also needed in order to reach significant scientific evidence which can be converted into dietary recommendations for CRC survivors.

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9 Papers I-III

I

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The Norwegian dietary guidelines and colorectal cancer survival (CRC-NORDIET) study: a food-based multicentre randomized controlled trial

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Abstract

Background: Colorectal cancer survivors are not only at risk for recurrent disease but also at increased risk of comorbidities such as other cancers, cardiovascular disease, diabetes, hypertension and functional decline. In this trial, we aim at investigating whether a diet in accordance with the Norwegian food-based dietary guidelines and focusing at dampening inflammation and oxidative stress will improve long-term disease outcomes and survival in colorectal cancer patients.

Methods/design: This paper presents the study protocol of the Norwegian Dietary Guidelines and Colorectal Cancer Survival study. Men and women aged 50–80 years diagnosed with primary invasive colorectal cancer (Stage I-III) are invited to this randomized controlled, parallel two-arm trial 2–9 months after curative surgery. The intervention group ($n = 250$) receives an intensive dietary intervention lasting for 12 months and a subsequent maintenance intervention for 14 years. The control group ($n = 250$) receives no dietary intervention other than standard clinical care. Both groups are offered equal general advice of physical activity. Patients are followed-up at 6 months and 1, 3, 5, 7, 10 and 15 years after baseline. The study center is located at the Department of Nutrition, University of Oslo, and patients are recruited from two hospitals within the South-Eastern Norway Regional Health Authority. Primary outcomes are disease-free survival and overall survival. Secondary outcomes are time to recurrence, cardiovascular disease-free survival, compliance to the dietary recommendations and the effects of the intervention on new comorbidities, intermediate biomarkers, nutrition status, physical activity, physical function and quality of life.

Discussion: The current study is designed to gain a better understanding of the role of a healthy diet aimed at dampening inflammation and oxidative stress on long-term disease outcomes and survival in colorectal cancer patients. Since previous research on the role of diet for colorectal cancer survivors is limited, the study may be of great importance for this cancer population.

Trial registration: ClinicalTrials.gov Identifier: NCT01570010.

Keywords: Colorectal cancer, Disease-free survival, Overall survival, Time to recurrence, Cardiovascular disease-free survival, Comorbidity, Inflammation, Oxidative stress, Antioxidant-rich foods, Food-based dietary guidelines

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Background

The incidences of colorectal cancer (CRC) are 5–10 times higher in Europe, North America and Oceania than in countries in Africa, south Asia and Central America [1], and the incidence in Norway is among the highest in the world [2]. Established risk factors for CRC are age, family history of CRC, inherited syndromes (Familial adenomatous polyposis, Lynch syndrome) and inflammatory bowel disease. In addition, several modifiable lifestyle-related risk factors are associated with CRC. Those include smoking, body fatness, abdominal fatness, diabetes, physical inactivity and an unhealthy diet (high consumption of alcohol, red and processed meat, and low consumption of foods containing dietary fibre) [3, 4]. World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) estimates that about 45% of all CRC cases could be prevented by improved lifestyle [3].

About 40% of CRC patients [5] have at least one concomitant disease (e.g. hypertension, cardiovascular disease (CVD), diabetes, chronic obstructive pulmonary disease or other malignancies) at the time of diagnosis and increased risk of developing additional comorbidities after CRC diagnosis [6–10]. These comorbid conditions may preclude or reduce effect of treatment, and consequently reduce disease-specific and total survival [8, 11, 12].

While it is well established that an unhealthy diet increases risk of CRC (e.g. see the latest update from World Cancer Research Fund, 2011 [4]) there are few studies that have focused on the effect of diet on disease outcomes and survival [13–15]. In paucity of data, health authorities in most countries recommend the same diet to CRC survivors (i.e. patients living with a CRC diagnosis, including those who have recovered) as to people without a cancer diagnosis [3].

Inflammation and oxidative stress are central underlying disease mechanisms in cancer and several other chronic diseases. Recent research suggests that there are two major molecular pathways leading to CRC, both of which involve inflammation and oxidative stress as major driving forces. The majority of CRC cases may be due to molecular events that result in chromosomal instability, while about 20-30% of CRCs are due to gene hypermethylation (called CpG island methylator phenotype (CIMP)) [16–18]. A large proportion of the CRC cases due to CIMP display microsatellite instability [18, 19]. In total, about 70 mutations in different genes have been identified as relevant for these two pathways to CRC, and it is assumed that each individual CRC tumor accumulates an average of 9 CRC pathogenic mutations out of this total pool of 70 mutations [16].

The heterogeneous pathogenesis of CRC comply with the hallmarks of cancer defined by Hanahan and Weinberg [20] and the cancer genome landscape as defined by Vogelstein et al [21]. Underlying these hallmarks of cancer, Hanahan and Weinberg proposed that genome instability and inflammation are two underlying driving forces [20]. These two processes or mechanisms are closely intertwined, since inflammation is a major cause of oxidative stress, and oxidative stress is a major cause of genome instability. Although inflammation and oxidative stress ultimately may be related to all CRC cases, the degree of inflammation and oxidative stress may vary significantly with the molecular signature present in the individual CRC patient [22].

In clinical trials and various models systems, we have identified a number of plant foods (e.g. berries, nuts, spices, coffee and specific fruits and vegetables) with the potential of dampening inflammation and oxidative stress [23–29]. Furthermore, a number of studies have also suggested that adherence to a prudent diet (e.g. Mediterranean diet) reduce inflammation and oxidative stress [30, 31]. We suggest that a prudent diet rich in specific plant-foods may be beneficial for CRC patients, especially those CRC cases with molecular signatures creating major inflammation and oxidative stress.

No intervention studies have investigated the role of diet in disease outcomes and survival in CRC-patients after diagnosis. Furthermore, no previous diet intervention study has focused on dampening inflammation and oxidative stress in this cancer population. This paper presents the background and design of a randomized controlled food-based diet intervention that examines the effects on disease outcomes and survival in CRC survivors. The diet intervention includes foods and drinks that have been suggested to dampen inflammation and oxidative stress. While specific anti-inflammatory and antioxidant-rich foods are emphasized in each food category, the complete intervention is fully in accordance with the prudent diet recommended by the Norwegian food-based dietary guidelines (NFBDG) [32] (i.e. a diet similar to the Mediterranean diet).

Objectives

Outcomes are inconsistently defined in many clinical cancer trials [33, 34]. For the primary outcomes, we have used the proposed guidelines for outcomes as described by Punt et al [34]. The two primary outcomes are (to be assessed when all patients have completed 5, 10, and 15 years, respectively, of follow-up after baseline):

1. Disease-free survival (DFS) (events are defined as detection of local recurrence or metastasis or any second cancer or death from any cause)
2. Overall survival (OS) (event is defined as death from any cause)

Secondary outcomes are:

I. Time to recurrence (events are defined as detection of local recurrence or metastasis)
II. CVD -free survival (events of CVD (ICD-10; chapter I) or death from any cause)
III. CRC-specific survival (death due to CRC)
IV. Total cancer-specific survival (death due to CRC or any other cancer)
V. Inflammatory disease-specific survival (death due to inflammatory disease)
VI. Cardiovascular (CVD)-specific survival (death due to CVD)
VII. New morbidity of other diet-related chronic diseases (e.g. ischemic coronary heart disease, cerebrovascular disease, thromboembolic disease, type 2 diabetes, obesity, hypertension and chronic obstructive pulmonary disease)
VIII. Dietary intake and nutritional status
IX. Physical activity and function
X. Nutrition biomarkers (e.g., carotenoids, fatty acids, 25-hydroxy vitamin D)
XI. Body composition
XII. Anthropometric measures (e.g. weight, waist and hip circumference)
XIII. Biomarkers for inflammation and oxidative stress (e.g. isoprostanes, cytokines)
XIV. Transcription- and epigenetic profiles
XV. Biomarkers for cardiovascular disease, metabolic syndrome, type 2-diabetes, thromboembolic disease and cancer (e.g. blood pressure, total/LDL-cholesterol, HbA1c, CRP, IL-6, IL-10, TNFα)
XVI. Health related quality of life and fatigue

The secondary outcomes will be assessed after 5, 10, and 15 years and described in detail in subsequent reports. In addition, intervention effects on secondary outcomes VII-XVI will also be assessed at 6 months, 1 year and 3 years follow-up.

Methods and Design

Study design

The CRC-NORDIET study is a multicentre, randomized controlled trial (RCT), with two parallel study arms. The intervention group receives an intensive dietary intervention and general advice on physical activity (see below), whereas the control group only receives standard general dietary advice and general advice on physical activity. Newly diagnosed CRC patients undergoing surgery are recruited to the study. In addition, an age-matched CRC-free reference group (will be published elsewhere) will also be included. The intervention starts 2–9 months after surgery (i.e. baseline), and consists of two periods: an intensive period that lasts 12 months, and a subsequent maintenance period which lasts an additional 14 years. Patients are invited to the study centre, situated at the Department of Nutrition, University of Oslo, at baseline, 6 and 12 months after baseline, and 3, 5, 7, 10 and 15 years after baseline. Additional follow-ups by regular mail, phone and e-mail, occur throughout the study. The study flow diagram is presented in Fig. 1. The design and handling of data of the CRC-NORDIET study is in fully agreement with the CONSORT statement [35].

Patients and eligibility

Men and women 50 to 80 years of age with newly diagnosed primary invasive colorectal cancer (ICD-10 18-20), staged I-III (TNM-staging system [36]) are eligible for the study. The patients must be able to read and understand Norwegian and to provide a signed informed written consent. Patients unable to perceive information and understand the intervention due to diagnosed dementia, or altered mental status as well as patients participating in other RCTs in conflict with our trial are excluded from the study. Precise inclusion and exclusion criteria are presented in Table 1.

Recruitment and randomization

Patients are recruited from Oslo University Hospital and Akershus University Hospital within the South-Eastern Norway Regional Health Authority. Screening for eligible patients is performed by research investigators in cooperation with hospital personnel by monthly reviews of surgery lists and medical records. Eligible patients are invited within 9 months from surgery.

Patients accepting the invitation sign an informed consent. Signed informed consent gives permission to the study personnel to take biological samples, perform physical measurements, and retrieve information from medical records, health registries and questionnaires. Information about storage of biological materials and use of individual data retrieved during the whole study for analysis and publishing purposes is also included in the informed consent letter.

Prior to baseline of the intervention, patients are randomized to either intervention group A or control group B in blocks of four. The random number sequence is computer-generated for each hospital. The person who generates the allocation sequence is neither the same person who determines eligibility nor the person that informs patients about their allocated study group. The patients are informed about the study group assignment at the baseline visit. Due to the nature of the intervention, neither the registered dietitians, nor the other research coworkers who meet the patients at the study centre, nor the patients themselves are blinded to group allocation.

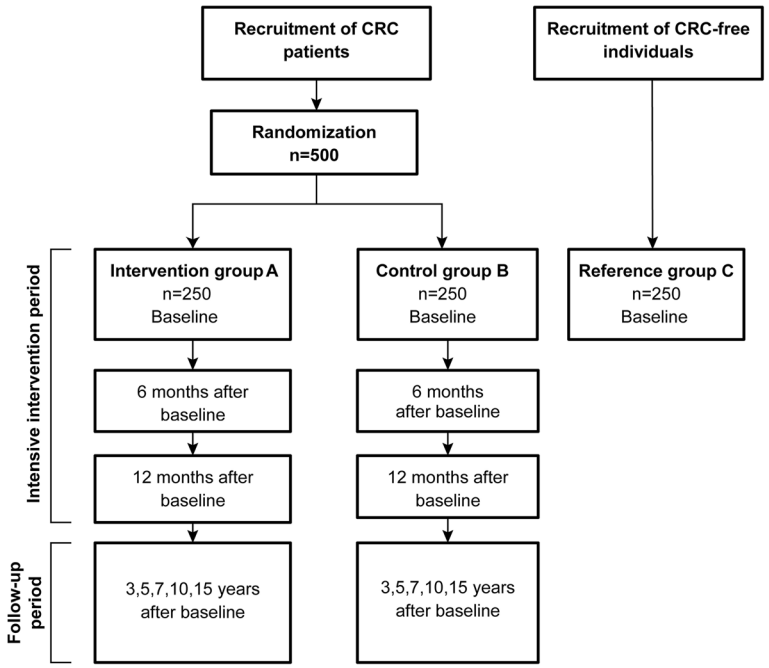

Fig. 1 Study flow diagram

Intensive period of intervention

The CRC-NORDIET study offers an extensive intervention program for patients in group A, consisting of individual counselling on nutrition and physical activity, grocery discount cards, delivery of free food items, group meetings, printed materials, access to a CRC-NORDIET webpage and contact by telephone and e-mail. The patients in group B are offered the same individual counselling on physical activity as group A, as well as general group meetings. An overview of the intervention program and the instruments used are presented in Table 2 and Table 3, and in Additional file 1.

Group A: diet intervention

Colorectal cancer patients experience different disease courses due to different stages at diagnosis, location of tumor, surgical procedure and adjuvant treatment. The diet intervention is therefore designed to meet the patients' individual needs after surgery. In the initial phase, when symptoms related to cancer and cancer treatment are most common, the dietary focus is mainly on recovery and treatment of symptoms and progressive weight loss. Later, when symptoms and weight loss are treated and under control, and the disease conditions are more stable, the major focus is long-term disease-free living and secondary preventions. In this phase, we emphasize a diet which may dampen chronic inflammation and oxidative stress, fully in accordance with the NFBDG. A number of strategies are implemented to improve compliance to the recommended diet of the CRC patients in group A (see below).

The dietary recommendations in the CRC-NORDIET intervention The NFBDG, published in 2011, was developed to prevent chronic diseases in the general population [32]. These guidelines are based on a comprehensive, systematic review of the evidence linking diet to risk of chronic diseases, including cancer. The guidelines do not provide a detailed diet plan, but define major aspects of the diet (Additional file 2). In the current study, the particular focus will be on the following NFBDG recommendations

1) daily intake of fruits, berries and vegetables (≥500 g/day)
2) weekly intake of 300-450 g fish
3) daily intake of 70-90 g wholegrains
4) limiting red and processed meat to maximum 500 g/week
5) keeping body weight within normal range of body mass index (BMI)
6) reduce intake of added sugar to < 10 E%
7) reduce salt intake to less than 6 g/day
8) achieving an average of at least 30 min of moderate (3–6 metabolic equivalents (METs)) physical activity per day or 150 min of moderate physical activity per week

The NFBDG can be implemented in different ways. For example, the recommendations of eating 500 g fruits, berries and vegetables every day may include different selections of individual foods, all compliant

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Primary adenocarsinoma colorectal cancer (ICD-10 C18-C20):
	C18 Malignant neoplasm of colon
	C18.0 Caecum
	C18.1 Appendix
	C18.2 Ascending colon
	C18.3 Hepatic flexure
	C18.4 Transverse colon
	C18.5 Splenic flexure
	C18.6 Descending colon
	C18.7 Sigmoid colon (sigmoid (flexure)
	C18.8 Overlapping lesion of colon
	C18.9 Colon, unspecified
	C19 Malignant neoplasm of rectosigmoid junction
	C20 Malignant neoplasm of rectum
	TNM stage I-III
	Age 50–80 years old
Exclusion criteria	Colorectal adenoma, carcinoid, abdominal carcinomatosis or sarcoma
	Unable to read and understand Norwegian
	Unable to perceive information and understand the intervention as such due to dementia or altered mental status
	Unable to follow the dietary intervention due to medical/clinical conditions e.g. total parental nutrition, permanently institutionalized
	Participation in another study in conflict with the intention of the CRC-NORDIET study

to the quantitative advice. However, not all of these foods may dampen inflammation and oxidative stress. Since inflammation and oxidative stress are ubiquitous as common basic pathogenic mechanism, we have selected to compose the intervention not only according to the NFBDG, but also by emphasizing those foods with strongest evidence for dampening low grade chronic inflammation and oxidative stress: We have identified foods and drinks that have high contents of redox-active compounds and/or have antioxidative effects individually or in combination in in vitro models, animal models, clinical trials and/or epidemiological studies [23–26, 28, 29, 37–56] (detailed list with references in Additional file 3):

- Drinks (e.g. coffee, black tea)
- Fruits and vegetables (e.g. onions, broccoli, tomatoes, carrots, pomegranates, garlic, oranges, olives)
- Berries (e.g. blueberries/bilberries, blackberries, and raspberries)
- Nuts (e.g. walnuts, almonds, and hazel nuts)
- Herbs and spices (e.g. thyme, oregano, clove, cinnamon, and rosemary)
- Whole grain (e.g. barley)
- Miscellaneous (dark chocolate)

Furthermore, we have also identified that the following foods and drinks may have anti-inflammatory effects individually or in combination in cell cultures, animal models, clinical trials and/or epidemiological studies (detailed list with references in Additional file 3):

Table 2 Instruments used to facilitate compliance in intervention group A during the first 12 months

	Baseline (at study centre)	1 month (at home)	3 months (at home)	6 months (at study centre)	9 months (at home)	12 months (at study centre)
Nutritional counselling	Face to face individual	Phone call	Phone call	Face to face individual	Phone call	Face to face individual
Free-of-charge food	Delivered at the visit		Home delivery	Delivered at the visit	Home delivery	Delivered at the visit
Information/ courses	Folder with information on the study and the study instruments	Inspiration day and Cooking course				
Discount card	Discount card (25% discount on healthy foods)					
CRC-NORDIET Webpage/ e-mail	Login-restricted webpage access and e-mail communication					
Physical activity	Access to free training facilities ("Pusterommet")					
Reports from non-biological measurements	Reports sent to the patients after every visit					

Table 3 Instruments used in the control group during the first 12 months

	Baseline (at study centre)	1–12 months (1, 3, and 9 months at home, 6 and 12 months at the study centre)
Information/ courses	Folder with information on the study	Inspiration day
Physical activity	Access to free training facilities ("Pusterommet")	
Reports from non-biological measurements	Reports sent to the patients after every visit	

- Coffee
- Fruits and vegetables (e.g. tomatoes, carrots, dog rose)
- Nuts (e.g. walnuts)
- Berries (e.g. strawberries, blueberries/bilberries, and blackberries)
- Whole grains
- Herbs and spices (e.g. thyme, oregano, and rosemary)

During the 15 year intervention period, these foods and drinks are gradually implemented in the advice to group A.

While these antioxidant- and phytochemical rich foods are advised as part of a balanced diet according to the NFBDG, patients were advised not to take any antioxidant supplements [55, 57].

Intervention strategies

The following instruments are used to facilitate compliance to the intervention in group A.

1. Individualized nutrition counselling by a registered clinical dietitian.

The nutritional counselling aims to meet the individual nutritional needs as well as educate the patients on how to change dietary habits in accordance with the NGBDG. In order to individualize the dietary advice, the registered clinical dietitian performs a comprehensive evaluation in each of the meetings (Fig. 1). The Patient-Generated Subjective Global Assessment (PG-SGA) tool [58] is used to assess nutritional status and nutritional impact symptoms. Weight and height measured the same day is used to calculate BMI, and current weight is compared with previous weight measurements to calculate weight changes. The presence of stoma is recorded as well as treatment status (i.e. whether or not the patient receives adjuvant treatment). Dietary intake is assessed by 24-h recall (at baseline). In addition, the registered clinical dietitian characterizes the patient's current diet in relation to the NFBDG, and record use of supplements.

When the nutritional evaluation is completed, the patient receives dietary advice based on nutritional status and weight history. If the patient is malnourished or at risk of malnutrition (i.e. PG-SGA category B or C), dietary counselling primarily focuses on improving nutritional status by treating symptoms, ensuring an adequate energy and protein intake, and to prevent further nutritional deterioration. In terms of progressive weight loss, patients with PG-SGA B or C with BMI >20 are recommended to stabilize their body weight. Patients with BMI < 20 are recommended to increase their body weight within the range of a normal BMI, determined in the current study as BMI 20–27 for patients aged 50–80 years [59, 60]. Well-nourished patients (i.e. PG-SGA category A) with BMI >27 are recommended to decrease their weight within normal BMI range. The recommended change (weight gain or weight reduction) is set to maximum 3 kg in 6 months to ensure an optimal change in body composition.

If the patient is evaluated as well-nourished (PG-SGA A), the dietary counselling primarily focuses on the NFBDG. Examples of week menus are used to illustrate examples of foods and amounts to be eaten in adherence with the NFBDG. Food alternatives are given to adjust the week menu to the patient's personal eating habits and preferences.

Motivation to change dietary habits in according to the NFBDG is recorded by asking whether the patient considers herself/himself to be either "very motivated", "motivated", "less motivated" or "not motivated". When one of the last two categories is present, the registered clinical dietitian explores the potential to increase motivation by using techniques from Motivational Interviewing (MI) [61]. The degree of motivation ("very motivated", "motivated", "less motivated" or "not motivated") is taken into account in each of the counselling sessions.

Each of the nutritional consultations is intended to result in a few dietary goals in agreement with the patient. It is emphasized that the patient defines her/his personal goals to increase the chances that he or she will succeed in changing dietary habits. The registered clinical dietitian aims at encouraging the patient to achieve these goals and the goals will be revised at next session. The telephone-based counselling in between the meetings at the study centre focus at monitoring the patient's body weight status, dietary pattern according to the predefined goals and motivational status. In addition to the scheduled consultations at the study centre and by telephone, the patients have the opportunity to contact the registered clinical dietitian by e-mail during the entire

intervention period. The same registered clinical dietitian follows the patient during the entire intervention period, when possible.

2. Discount card (25% discount on healthy foods)

The patients in the intervention group are offered a discount card from the retailer company, "Norgesgruppen", which is Norway's largest enterprise within the grocery market, with a market share of 40%. The discount card can be used within the first year of the intervention and gives a 25% discount on all fresh vegetables, fruit, berries and fish and on all food items marked with the keyhole symbol, which is used by the health authorities to label food that is considered the most healthy within its food category [62]. The discount card can be used in all food stores and supermarkets within "Norgesgruppen".

3. Delivery of specific foods

The CRC-NORDIET is sponsored by several food producing companies with free food items, specifically selected in accordance with the anti-inflammatory and antioxidant-rich foods emphasized in this study, such as juice, garlic, tomato juice, fish, coffee, tea, cereals, whole grain bread, oils etc. At all visits to the study centre, the patients in group A receive a bag containing a mixture of these food items. In addition, they receive a box with free food items delivered to their homes two times during the intensive period of the intervention.

4. CRC-NORDIET website

The patients in the intervention group get access to a login-restricted, dynamic website with detailed information about the NFBDG, portion sizes of recommended intake of fruits and vegetables and whole grain, food recipes, examples of week menus, dietary advice for treatment-related symptoms and advice on physical activity. In addition, information about the CRC-NORDIET study and contact information for the study organizers are given. The website is continuously updated.

5. Printed materials

The patients in the intervention group receive printed materials at the first visit to the study centre and at all follow-ups to ensure that also patients who do not use the internet get all relevant information.

6. Cooking course

During the first 6 months of the intervention, each patient in group A is offered a one-day cooking course. This course is led by a registered clinical dietitian who follows a protocol developed for the CRC-NORDIET intervention. The aim of the cooking course is to give the patients practical experience in making healthy dishes and to introduce healthy choices when shopping for food. The course consists of a one hour lecture on the NFBDG and how to implement these guidelines in daily cooking. All recipes can also be found on the CRC-NORDIET web site.

7. Physical activity

The CRC-NORDIET study has an agreement with "Active against cancer" [63], a non-governmental non-profit organization founded in 2007. The organization operates a free training studio ("Pusterommet") for cancer patients at several hospitals in Norway. The physical therapists working at these studios are instructed to give individualized advice for exercises during and after cancer treatment. The CRC-NORDIET patients are encouraged to utilize this offer.

Moreover, the CRC-NORDIET patients are advised to practice moderate physical activity for at least 30 min per day, or 150 min per week, and they receive a booklet on how to be physically active in daily life. In addition, they are recommended to use local facilities, including swimming pool, health training centres and walks in their neighbourhoods.

8. Inspiration day

The patients in Group A are invited to an inspiration day within the first 6 months of the intervention. The day opens with a 45 min lecture about the aim and background of the CRC-NORDIET study by the project leader, with special focus on the NFBDG. The patients are shown examples of different portion sizes of fruits and vegetables, nuts, whole grain products, the food-dish-model, and have the opportunity to talk to registered clinical dieticians. The last part of the inspiration day focuses on physical activity, and starts with a lecture about physical activity incorporated in daily life. The patients also meet the physical therapists from "Pusterommet". The meeting ends with a lunch and a quiz about physical activity, and each patient receives a pedometer as an incentive to be physically active.

9. Written reports

The patients receive reports from the non-biological samplings (e.g. anthropometric measurements and blood pressure, described in detail in the following section) performed at the three time points during the intensive intervention period (baseline, 6 and 12 months after

baseline), as well as a one-year report showing the development during the last year. Reports from the physical activity monitors are given to the patients after the first intensive year of intervention.

Group B: control group

1. Physical activity

Patients in the control group receive the same basic advice on physical activity as well as free access to the training studio as patients in the intervention group (see above).

2. Inspiration day

The inspiration day is structured identically as for group A, except for the session focusing particularly on diet, which is excluded in the inspiration day for group B.

3. Dietary information

The patients in group B receive a booklet with basic dietary advice at baseline. In contrast to the intervention group, the control group receives no individualized dietary advice adapted to their eating habits and preferences. If they seek counselling concerning symptoms related to cancer or cancer treatment, the registered clinical dietitians provide dietary advice based on information from booklets and other printed materials already available in the hospitals. This information and dietary advice is considered as part of the standard care.

4. Written reports

The patients in group B receive written reports similarly as group A after all visits during the intensive intervention period.

Moderate intervention during maintenance period (year 2–15)

During the maintenance period, which starts after the first intensive year and lasts for 14 years, both groups receive reports (e.g. anthropometric measurements and blood pressure) following every visit at study centre (year 3, 5, 7, 10 and 15).

The patients in group A are invited to an inspiration day every year during moderate period of intervention. The aim of these meetings is to maintain the focus on foods dampening inflammation and oxidative stress and the NFBDG, and to encourage the patients to continue following the guidelines in a long-term perspective. In addition, group A are offered dietary counselling at each visit at the study centre, as well as a telephone counselling by the registered clinical dietitians once a year. They also have access to the CRC-NORDIET webpage which is continuously updated with information and encouragements (e.g. recipes, nutrition information, motivational tips and relevant popular reports from nutritional sciences) until the end of study participation. An overview of the instruments used during the maintenance period is presented in Table 4.

Assessment of primary outcomes

Several registries and medical records will be used for assessment of primary outcomes. The registries and time points for primary outcome assessment are summarized in Table 5.

Questionnaires, biological samplings and measurements

Group A and Group B are undergoing equal regimes of measurements and biological samplings at all visits (Additional file 4). All patients are also asked to complete several questionnaires regarding demographic information, dietary intake, health status and physical activity (described below) (Additional file 4). The questionnaires administered at baseline of intervention are also completed at 6 months and 12 months follow-up. After the first year, the patients are invited to the study centre for questionnaires, biological samplings and measurements 3, 5, 7, 10 and 15 years after baseline. In addition to the visits to the study centre during the maintenance period, finger prick blood sample equipment (dried blood-spot cards) and questionnaires are sent to the patients' home at certain time points and subsequently returned to the study centre.

Demographic information

A short questionnaire is used to assess demographic characteristics including age, gender, marital status, ethnicity, level of education, working status, family history of CRC or other type of cancer.

Table 4 Instruments offered to the respective groups during maintenance period of intervention

Instruments	Time points	
	2, 4, 6, 8, 9, 11, 12, 13, 14 years	3, 5, 7, 10, 15 years
Dietary counselling at study centre (Group A)		X
Dietary counselling by telephone (Group A)	X	X
Inspiration day with extended diet session (Group A)	X	X
CRC-NORDIET Website/e-mail (Group A)	X	X
Reports from non-biological measurements (Group A and B)		X

Table 5 Data source used to assess primary outcomes

Outcome	Instrument	5 years after baseline	10 years after baseline	15 years after baseline
DFS	Colorectal Cancer Registry of Norway, Cancer Registry of Norway, Cause of Death Registry in Norway, Norwegian Patient Registry, Norwegian Prescription Database	X	X	X
OS	Cause of Death Registry in Norway	X	X	X

DFS disease-free survival, *OS* overall survival

Assessment of dietary intake

Semi-quantitative food frequency questionnaire (FFQ) The semi-quantitative 282-item FFQ used in CRC-NORDIET is designed to assess habitual diet over the preceding year, including both frequency of intake and portion sizes. The FFQ is described and validated elsewhere [64, 65].

Compliance questionnaire The compliance questionnaire is a semi-quantitative short 63-item FFQ, developed within this study and designed to assess the dietary intake (grams per day) and physical activity (minutes per day) for the last 1–2 months. The questions correspond to the food groups and the recommendations regarding physical activity of the NFBDG. The questionnaire will be validated within the first period of study.

Food records Food intake is recorded by using a 7-days weighed food record. The patients are provided with a food diary and a digital scale, and are instructed on how to weigh and record all foods and beverages consumed during a period of seven days. The food diary include all days of a week, and can either record seven consecutive days or be divided into two periods of three and four days within two weeks. The food records are performed in a subgroup of patients (will be published elsewhere).

24-h recall A registered clinical dietitian performs a 24-h recall at baseline by asking the patients in the intervention group in details about the intake of foods and drink during the past 24-h period. The 24-h recall is performed only in intervention patients since it is an integrated part of the nutritional counselling.

Assessment of physical activity and function

Recording of daily physical activity The physical activity monitor SenseWear Mini Armband (BodyMedia, Pittsburgh, Pennsylvania, USA) [66] is used to record daily physical activity, inactivity and energy expenditure during seven consecutive days among all patients in both study arms at all visits. The armband monitors physiological data such as heat flux, galvanic skin response, 3-axis accelerometer and skin temperature. All data are retrieved from the armband to the computer with the SenseWear Professional Software [66]. The participant are instructed how to use the armband, and return it in a stamped envelope to the CRC-NORDIET study at the end of the test period. The armband is pre-programmed with the co-predictors such as weight, height, age, gender, smoking status (smoker/non-smoker) and placed around the non-dominant arm.

Self-reported physical activity The patients are asked to complete a questionnaire regarding frequency, intensity and duration of their daily physical activity, as well as duration of sedentary time. These questions are based on the questionnaire from the HUNT 3 study in Norway [67].

6-min walking test Patients are invited to a 6-min walk test (6MWT) at several time points. The test is performed indoors, along a long, flat, straight, enclosed corridor with a hard surface. The walking course is 30 m in length, and cones mark the turnaround points. A countdown timer (or stopwatch) is used to record the time of the test. Prior to the test, the researcher measures the blood pressure of the patient. In addition, the pulse is monitored before, during and after the test. The patients are asked to grade its level of shortness of breath and the level of fatigue by using the Borg scale 6-20 before and after the test. Total length of walking (in meters) is recorded during 6 min of time.

Sit-to-stand test The test is performed by the use of a straight back chair with a solid seat at the height of 44 cm. The patients are instructed to sit on the chair with arms folded across their chest, and then to stand up and sit down as quickly and frequently as possible within 30 s, keeping both arms folded across the chest. The number of stands during this period is counted.

Handgrip strength Hand-grip strength is measured by the MAP 80 K1 Hand grip dynamometer (KERN & SOHN GmbH, Balingen, Germany) and measured as described in the manufacturer's protocol [68]. The maximal strength of hand grip (kg) is recorded. For women and men, a 40 kg- and 80 kg-spring is used, respectively. The grip strength is measured with one punch and repeated three times on both hands. The maximum handgrip strength on both left and right hands are recorded.

Assessment of nutritional status

Patient-Generated Subjective Global Assessment (PG-SGA) Nutritional status is measured by using the scored PG-SGA [58], a nutritional assessment tool specifically developed and validated for cancer patients. A

translated (Norwegian) version is used. Both the global categories well-nourished (A), moderate malnourished (B) and severe malnourished (C), as well as the numerical scoring system are used to characterize the nutritional status.

Anthropometric measurements

Body weight Body weight (kg) is measured by using a non-slip Marsden M-420 Digital Portable Floor Scale (Marshden, Rotherham, South Yorkshire, United Kingdom) or a digital wireless measuring station for height and weight, Seca 285 (Seca, Birmingham, United Kingdom) [69]. Measurements are performed with light clothes and without shoes. Body weight is recorded with 2 decimals and the kind of clothing is recorded.

Height Height (cm) is measured using either a mechanical height rod (Kern MSF- 200, [68]) or a digital wireless stadiometer (Seca 285 [69]). The height is recorded with one decimal precision.

Waist and hip circumference Waist circumference is measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, whereas the hip circumference is measured around the widest portion of the hips. Waist and hip circumference are used to calculate the waist hip-ratio (WHR) which is a well-established indicator of abdominal fatness [70].

Body composition analysis

Bioelectrical impedance analysis (BIA) BIA is performed under standardized conditions by the use of BIA 101 (SMT Medical, Würzburg, Germany) that applies a current of 0,8 μA at a frequency of 50 kHz. Four skin electrodes are placed on hand and foot of the patients when lying in supine position. All measurements are conducted on the patients' right side as instructed by the manual. Resistance (Rz) and reactance (Xc) are used in appropriate and validated equations to calculate body composition compartments such as fat mass, fat free mass and muscle mass. In addition, BIA is also performed with Seca mBCA515 (Seca, Birmingham, United Kingdom) [71]. Patients carrying a pacemaker are excluded from the BIA measurements.

Dual-energy x-ray absorptiometry (DXA) The Lunar iDXA (GE Healthcare Lunar, Buckinghamshire, United Kingdom) is used to measure bone mineral density and body composition, including quantification of visceral fat.

Computed tomography (CT) CT images taken routinely for clinical purposes are used for body composition analysis, i.e. quantification of fat (visceral, subcutaneous and intermuscular adipose tissue) and skeletal muscle. The images are analysed using the Slice-o-matic software, version 4.3 (Tomovision, Montreal, Canada). The third lumbar vertebra (L3) is chosen as standard landmark since skeletal muscle, lean tissue mass and adipose tissue at this level are significantly correlated to whole-body tissue in healthy adults [72].

Blood pressure

Blood pressure (BP) is measured with the digital blood pressure patient monitor Carescape V100 (GE Healthcare, Fairfield, USA) and performed by trained staff following the clinical procedure as described by the manufacturer [73]. After a 5 min resting period in a silent room, BP is measured four times on the non-dominant arm with intervals of one minute.

Biobank

A variety of biological samples will be collected at different time points during the study and will be used for the purposes of measuring surrogate outcomes, biomarkers of food intake and for identification of phenotypes associated with different responses to the intervention.

Venous blood samples Overnight fasting blood samples are taken between 07.30 and 10.30 at the study centre by a trained technician. BD Vacutainer® (Becton, Dickinson and Co, Franklin Lakes, NJ, USA) tubes are used to collect ethylene diamine tetraacetic acid (EDTA) samples (no. 367861 and 366643), serum samples (no 368774), lithium heparin samples (no 367526), and citrate samples (no 369714).

Serum tubes are placed in room temperature for 30 min. Serum, EDTA and heparin samples are centrifuged at1500 *g*, 10 min, 15 °C. Serum, plasma and red blood cells are aliquoted, and immediately stored in at −80 °C until further analysis. Whole blood from EDTA samples are also aliquoted for e.g. DNA extraction and DNA damage/repair analysis The buffy coat from the heparin samples are either frozen at −80 °C for later analysis or used to obtain isolated peripheral blood mononuclear cells (PBMC) through Percoll centrifugation. The isolated PBMCs from heparin samples are used for *ex vivo* experiments. Two citrate tubes are kept 1 h respectively at 4 °C and room temperature before centrifugation (2500 *g*, 15 min, 4 °C) to obtain core plasma, plasma and red blood cell aliquots that are stored at -70 °C. One citrate tube is centrifuged (2500 *g*, 15 min, 4 °C) within 30 min of sampling, and core plasma is stored at - 80 °C for further analysis of thromboembolic factors. The citrate buffy coats are used to obtain isolated PBMCs for the study of DNA repair and DNA damage. PAXgene Blood RNA Tubes (cat.no 762115, PreAnalytiX, Hombrechtikon, Switzerland) are used as source for total blood RNA. The tubes are kept 2 h at

room temperature before they are frozen at -20 °C for 24 h and subsequently transferred to −80 °C until time for RNA isolation.

Isolation of buffy coats from EDTA samples The EDTA buffy coats are re-solved in 9% NaCl (cat.no 586564, B.Braun Melsungen AB, Melsungen, Germany) solution before added on top of 4 ml Lymphoprep (cat.no 1114545, Axis-Shield, Oslo, Norway) in a 15 ml tube for centrifugation (20 min RT 400 g) to isolate PBMCs which are further used for a chromatin crosslinking procedure. The crosslink procedure for preparing the cell pellets for ChIP-chip analysis are performed as follows: Firstly, PBMCs are allowed to crosslink with 1% formaldehyde (final concentration) for 10 min at room temperature, adding glycine (0.125 M) for 10 min at room temperature to stop the crosslinking process. After washing the cell pellets twice with 10 mL of ice-cold 1 × PBS the pellets are immediately stored in 2 ml plastic tubes at −80 °C until proceeding further with protocols for Chip-on-Chip analysis at a later time point.

Finger prick blood samples Finger prick blood samples for analysis of e.g. biomarkers of dietary intake, oxidative stress and oxidative damage are collected by the dried blood spots (DBS) method as previously described [74]. DBS cards (2 cards per patient) are allowed to dry in room temperature for 2 h and are frozen at −80 °C in airtight aluminium bag with a desiccant until further analysis.

Urine samples Biomarkers of food intake, oxidative stress and other risk factors related to the progression of CRC will be measured in urine. Urine samples are collected from a subpopulation several times during the intervention by the methods as previously described [75–77].

Faeces samples Microbiotica and biomarkers related to CRC will be measured in faeces samples which are collected from a subpopulation several times during the intervention. The patients will receive a specific faeces sample tool kit and are asked to collect the sample at home and mail it to the study centre. Sampling and analysing of the faeces samples will be performed by following the procedure as described by Naseribafrouei [78].

Tumour tissue Molecular signatures in CRC tumours that are linked to inflammation, oxidative stress and energy balance have been shown to predict response to lifestyle intervention. Characterization of tumor markers will be performed by immunohistochemistry, PCR, sequencing and q-PCR (to be published elsewhere). Furthermore, we will study whether tumor markers predict response to the dietary intervention. Samples of tumor tissue are collected at surgery in collaboration with the hospitals. Molecular signature data are also obtained from the CRC biobank project at the Oslo University Hospital.

Oral glucose tolerance test

Prior to the oral glucose tolerance test, the patient is fasting for at least 8 h. Blood samples (serum and PAX tubes) are taken, and blood glucose is measured with a blood glucose meter [79]. The patients are asked to drink 75 g of glucose (D (+)-Glucose (product number: 1370485000, Merck-Millipore Corp, Darmstadt, Germany) in 4 dl of boiled water. The glucose liquid is expected to be consumed total within 5 min. Blood samples will be taken after 2 h. Exclusion criteria for oral glucose tolerance test are Diabetes Type I, use of insulin and/or fasting blood glucose level exceeding 10 mmol/l.

Health related quality of life and fatigue

Quality of life will be self-reported and measured using the generic, multi-purpose-form questionnaire for Health related quality of life (HRQOL) called Short form (SF) health survey consisting of 36 items (SF-36) [80]. The 36 items are categorized into eight multi-item scales; 1) physical functioning, 2) role physical, 3) bodily pain, 4) general health, 5) vitality, 6) social functioning, 7) role emotional and 8) mental health as well as a single-item measuring health transition during the last year. The data will first be standardized in order to compare results across studies [80] and then recoded according to a syntax developed by Loge et al [81].

A validated generic fatigue questionnaire (FQ) is used to assess the patients subjective fatigue status (11 items) and the duration and extent of fatigue (2 items) [82]. The FQ asks about fatigue symptoms experienced during the last month compared to how the subject felt when she/he was last feeling well [82–85]. Each item has four response-choices [82]. The scoring of each response is based on a Likert- (0, 1, 2, 3) and a dichotomized (0, 0, 1, 1) scale. The latter is only used for case definition. The total sum of the Likert-scores is designated total fatigue (TF) where higher scores imply more fatigue.

Assessment of new morbidity of diet-related chronic diseases and adverse events

New morbidity of diet-related chronic diseases arising after CRC diagnosis (e.g. ischemic coronary heart disease, cerebrovascular disease, thromboembolic disease, diabetes, hypertension and chronic obstructive pulmonary disease) will be collected from the national health registries in Norway, a comorbidity questionnaire developed for this study designed to assess comorbidity based on data from the third Norwegian population health study (HUNT 3) [67], and from medical records. These

data will be supplemented by data on drug use from the Norwegian Prescription Register. Adverse events are recorded based on the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0) [86].

Sample size

Calculation for primary outcomes

The sample size calculations are based on assuming a Weibull distribution for the survival times in both arms. We further assume a constant hazard ratio for the intervention effect over time and that we have the same follow-up of 5, 10, or 15 years, respectively, for all patients. Sample sizes required to achieve a statistical power of 80% and significance level of 5% were calculated with computer simulations using the spower function in R (version 3.2.0) package Hmisc version 3.17–0. Survival rates in the control group [2, 87] and expected reduction in mortality rates in the intervention group are taken from the literature (see Discussion, [88–93]). With a 68% 5-year OS in the control group, we have 80% power to detect a 25% reduction in mortality due to the intervention (corresponding to a hazard ratio of 0.71). The required total sample size is then 500 (250 in each study group) (Table 6).

Moreover, sample size calculation based on 25% reduction in events of DFS after 5 years of surgery (59% 5-year DFS in the control group), we have 80% power to detect HR of 0.70, with 190 patients in each group (Table 6).

Table 6 Sample size in each group (n) and hazard ratios (HRs*) for selected scenarios of reduction in mortality by intervention. The power is 80% and significance level 5%

	Reduction in mortality by intervention			Survival rates in the control group
Primary outcome	*20%*	*25%*	*30%*	
	n (HR)	n (HR)	n (HR)	
DFS				
5 years	320 (0.753)	190 (0.696)	140 (0.641)	0.59
10 years	240 (0.716)	140 (0.655)	110 (0.597)	0.41
15 years	180 (0.680)	120 (0.616)	90 (0.557)	0.29
OS				
5 years	390 (0.767)	250 (0.712)	160 (0.658)	0.68
10 years	280 (0.732)	180 (0.673)	130 (0.616)	0.48
15 years	210 (0.695)	140 (0.632)	100 (0.574)	0.34

* HR = hazard ratio of intervention versus control, which corresponds to the assumed survival rate in the control group and assumed reduction in mortality by intervention

DFS disease-free survival, *OS* overall survival

Stratified and subgroup analysis

All of the power calculations are based on a heterogeneous population of CRC patients.

Since post-surgery treatment may vary, and colon versus rectum cancer may respond differently to the diet intervention, we will also perform stratified statistical analysis. It is not known whether treatment effects are different in these subgroups. These stratified analyses will be conducted with primary outcomes at the later time-points in the study and at all time-points to assess mean differences between the control and the intervention groups in biomarker analysis, as these data normally require fewer patients per group.

Statistical analysis

Data will be analysed using SPSS (IBM SPSS Statistic 22). For the survival outcomes (primary outcome 1 and 2, and secondary outcomes I-VI) tests will be performed to compare survival rates between the control and intervention groups at 5, 10, and 15 years after baseline. Survival probabilities will be estimated with the Kaplan-Meier method. Cox proportional hazards models will be used to identify prognostic and predictive biomarkers for survival outcomes.

For non-survival secondary outcomes, parametric or non-parametric tests for two-group comparisons will be used to assess group differences at individual time-points. In addition, mixed effect models for longitudinal data and regression models will be used to evaluate association and change over time in dietary intake, nutritional status, body composition, molecular tumor characteristics, physical function and activity, quality of life, fatigue and treatment related outcomes and to examine differences between the intervention and control groups. All statistical tests are performed as two-sided tests. Effects are considered statistically significant if $p < 0.05$.

Discussion

The primary aims of the CRC-NORDIET are to study whether a healthy diet rich in anti-inflammatory and antioxidant-rich foods and based on the NFBDG can improve DFS and OS in CRC patients. To our knowledge, this is the first randomized controlled trial designed to investigate the effect of a dietary intervention on these outcomes in CRC patients, and to investigate the potential role of diet in dampening of inflammation and oxidative stress in these patients. The multiple strategies used to achieve compliance to the intervention during the first year, followed by the 14 years maintenance and follow-up period make the design of this intervention unique.

Data on role of diet on disease outcomes and survival in CRC survivors is limited. To date, several cohort studies, but no RCTs have investigated the effects of food-based dietary interventions on these outcomes.

Data from a US cohort study with stage III colon cancer patients suggest that high intakes of red and processed meat, fat, refined grains and dessert, i.e. a Western dietary pattern, after diagnosis are associated with a significantly reduced disease-free and OS [13]. Similar findings are reported in a Canadian cohort study with CRC patients staged I-III, where patients with the highest intake of processed meat the previous year before diagnosis had an 82% increased risk of recurrence or death compared with patients with the lowest intake [15].

Prospective cohort studies have consistently reported that physical activity after colorectal cancer diagnosis reduces risk of mortality. In a meta-analysis of six prospective cohort studies, including 7522 CRC survivors, the authors observed that the most physical active survivors had a 42% lower risk of total mortality compared to those who were least active. The risk reduction of cancer-specific mortality was 39% [94]. No RCT has so far confirmed that physical activity impacts mortality in CRC survivors.

Interventions designed to investigate the effect of diet separated from other lifestyle factors (smoking, physical activity, weight regulation) are needed in order to investigate whether there is a causal relationship between diet and survival as well as disease-related outcomes. Our intervention is intended to change the dietary habits towards a diet in agreement with the NFBDG. These dietary guidelines are developed to prevent chronic diseases, including cancers, in the general population. Several large cohort studies have shown that there is a consistent inverse association between adherence to cancer prevention guidelines and cancer-specific and all-cause mortality [89, 95]. Among cancer survivors, reduction in total mortality between highest versus lowest score in adherence to diet recommendations has been documented in five different cohort studies, ranging from 24% to 36% (follow-up period from 3.7 to 13.6 years) [88–93]. Association of adherence to American Cancer Society guidelines and reduction in death attributed to cancer has been shown to be 25 and 26% in men and women, respectively [89]. Hastert et al documented an association of adherence to the WCRF/AICR guidelines and reduction in cancer-specific mortality of 61% in respondents with the highest compared to the lowest WCRF/AICR score (follow-up time of 7.7 years) [95].

Furthermore, NFBDG include advice regarding red and processed meat, dietary fibre, dairy products and garlic, all of which are related to risk of CRC. Whether these dietary factors also may have effect on survival and disease outcomes, remain unclear. With improvement in cancer survival, these perspectives are increasingly important. The main objective of the present study is to test if diet will improve survival and cancer-related outcomes, mediated through reduced inflammation and oxidative stress. To strengthen this assumption, we have chosen to select specific foods within the NFBDG which have been identified as anti-inflammatory or antioxidant-rich in previous preclinical and clinical studies [23–29, 37–39, 41–48, 53, 55, 96].

Four aspects that may be of importance for achieving lifestyle changes and facilitate compliance to the intervention: 1) timing of intervention, 2) choice of motivational approach to achieve lifestyle changes, 3) duration of intervention, and 4) use of incentives and methods to achieve sustainable changes. Previous studies have shown that cancer patients in general are particularly motivated to change dietary habits at the time of diagnosis, often reported as the teachable moment [97–99]. Interventions designed to include this teachable moment have shown to be successful [97–99]. In our trial, we introduce the dietary intervention within a few months from surgery, thereby expecting we reach the patients within the time frame of this teachable moment. Furthermore, principles from MI [61] are implemented in each of the dietary counselling sessions by trained registered clinical dietitians. Previously published trials that have succeeded in changing lifestyle behaviours in cancer patients are based on theoretical frameworks and theories, including social cognitive behaviour therapy and use of MI. It is emphasized that the patient defines her/his own goals to increase the chances that he or she will succeed in changing dietary habits. We suggest that it is important to focus on a few realistic goals at the time, instead of aiming at changing the whole diet immediately. In addition, follow-up by the same registered clinical dietitian during the entire intensive intervention period may be of importance for the commitment to the intervention goals.

In order to increase the chances of sustainable lifestyle changes and compliance to the intervention, our intervention consists of a one year intensive period and a subsequent maintenance period which lasts for until 14 years. Taking into account that the teachable moment may vary among the patients and it may take time to establish new sustainable dietary habits, the inclusion of a maintenance period will probably be beneficial with regard to an increased long-term adherence to the intervention. Previous published trials that have failed in compliance from the patients may have had too short time frame of diet intervention.

Different strategies are reported to be effective in promoting lifestyle changes in cancer survivors [14, 97, 98, 100, 101]. Interventions focusing on individual counselling [14, 98, 100], and also interventions with a mixed strategy of individual in-person counselling, telephone counselling and mailed materials [97, 101] have been shown to be effective in health behaviour change among CRC survivors. Thus, during the first year, the CRC-

NORDIET study offers individualized counselling, free foods, a discount card on healthy foods, access to a login-restricted web page, printed materials, cooking courses and inspiration day, which may all be effective incentives to follow the NFBDG.

In placebo-controlled RCTs, an intervention is tested by comparing one group of individuals who receive the intervention with a control group who receives a placebo. This type of placebo-controlled RCT is most often not possible when studying food-, or exercise-based interventions, since placebo-foods or placebo-exercise do not exist. In addition, no food based intervention can be analysed thoroughly without considerations regarding energy intake and energy expenditure. We have therefore selected to give the intervention group and the control group the same advice on physical activity. We include careful monitoring of physical activity to control for any confounding effects of physical activity. Of ethical reasons, we also include standard dietary advice (i.e. standard clinical care) in the control group, as well invitations to group meetings and feed-back reports on health status. Thus, while the control group in the present study is not identical to a placebo group, this particular study design was used in order to isolate the effect of diet intervention on CRC patients, and to reduce drop-outs from the control group, which is a common concern in long-term intervention trials.

Sample size estimation is not straightforward in RCTs with complex diet intervention and long term hard outcomes. This is especially the case when no similar trials have been previously published. By using the best available information from scientific literature and Norway Cancer Registry on survival rates in the control group and expected reduction in mortality rates in the intervention group, we have performed power calculations on the two primary outcomes after 5, 10 and 15 years after baseline. We conclude that 250 patients in each group would give us a reasonable chance (at 80% power) to detect any significant effects (see Methods and Design section for details) after 5, 10 and 15 years.

In a similar study, testing the effects of two different 6 months adjuvant cytostatic protocols (i.e. the MOSAIC study [102]), 2246 patients who had undergone curative resection for stage II and III colon cancer, were recruited. After a median follow-up for 38 months, fewer cancer-related events was observed in the alternative treatment group compared to the standard treatment group (HR 0.77, $p = 0.002$). The main reason for the lower number of patients required in our CRC-NORDIET study compared to the MOSAIC study is due to an older population with more expected events (50–80 years versus 19–75 years) and a longer follow-up time (10 and 15 years versus 3 years).

We have also performed a number of power estimations on secondary outcomes (data not shown). In general, the CRC-NORDIET study is expected to have enough statistical power to detect significant effects in a majority of these intermediate outcomes (to be published in relevant reports). These power calculations on primary and secondary outcomes are also supported from the RCTs with physical activity intervention in CRC and breast cancer patients; Friedenreich and Courneya detected significant effects on intermediate outcomes (e.g. inflammation biomarkers) as well as disease outcomes in RCTs with 200–250 patients per group [103–105].

Conclusion and perspectives

The CRC-NORDIET study investigates whether a diet aimed at dampening inflammation and oxidative stress and in full accordance with the NFBDG will improve survival and disease outcomes in CRC patients. This RCT is unique in several aspects related to the interventions as well as outcomes. Since previous research on the role of diet for CRC survivors is limited, the study is important in order to improve health outcomes and survival in this population.

Additional files

Additional file 1: The CRC-NORDIET intervention program (DOC 42 kb)

Additional file 2: Summary of the 13 recommendations of the Norwegian food-based dietary guidelines (NFBDG) (directly translated from the NFBDG) (DOCX 23 kb)

Additional file 3: Detailed list of foods and drinks with high contents of redox-active compounds and/or antioxidative effects (DOCX 22 kb)

Additional file 4: Questionnaires, biological samplings and measurements (DOC 43 kb)

Abbreviations

6MWT: 6-min walking test; ACS: American Cancer Society; AICR: American Institute of Cancer Research; BIA: Bioelectrical impedance analysis; BMI: Body mass index; BP: Blood pressure; CIMP: CpG island methylator phenotype; CRC: Colorectal cancer; CRP: C-reactive protein; CT: Computerized tomography; CTCAE: Common terminology criteria for adverse events; CVD: Cardiovascular diseases; DBS: Dried blood spots; DFS: Disease-free survival; DNA: Deoxyribonucleic acid; DXA: Dual-energy x-ray absorptiometry; EDTA: Ethylene diamine tetraacetic acid; FFQ: Food frequency questionnaire; FQ: Fatigue questionnaire; HbA1c: Glycated hemoglobin A1c; HR: Hazard ratio; HRQOL: Health related quality of life; HUNT: Helseundersøkelsen i Nord-Trøndelag; ICD: International classification of diseases and related health problems; IL: Interleukin; L3: Third lumbar vertebra; LDL: Low density lipoprotein; METs: Metabolic equivalents; MI: Motivational interview; NFBDG: Norwegian food-based dietary guidelines; OS: Overall survival; PBMC: Peripheral blood mononuclear cell; PG-SGA: Patient-Generated Subjective Global Assessment; RCT: Randomized controlled trial; RT-PCR: Real-time quantitative reverse transcription polymerase chain reaction; SF-36: Short form-36; TNFα: Tumor necrosis factor alpha; TNM: Tumor Node Metastases; WCRF: World Cancer Research Fund; WHR: Waist hip-ratio

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Availability of data and materials
Anonymized data resulting from this study may be available upon request by corresponding author.

Authors' contributions
HBH and HR had a main responsibility for writing the manuscript. SKB, IP, ASK, SÅB, MTE, GW, IE, AF, MBV, MZ, SS and RB contributed to the study design and protocol. RB is the principal investigator. All authors contributed to the writing and approval of the final manuscript.

Competing interests
R.B. is a shareholder in the company Vitas AS. The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study is approved by the Regional Committees for Medical and Health Research Ethics (REC Protocol Approval 2011/836) and by the data protection officials in Oslo University Hospital and Akershus University Hospital. All biological materials are stored in a biobank at University of Oslo. The biobank will expire in 2040 (according to the REC approval). The study is registered on the National Institutes of Health Clinical Trials (www.ClinicalTrials.gov; Identifier: NCT01570010). Written informed consent to participate has been obtained from the patients enrolled in the CRC-NORDIET study.

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Additional file 1. The CRC-NORDIET intervention program

	Intervention group	Control group
Dietary counselling by a registered clinical dietitian	Individual counseling at all visits at the study center. Telephone dietary counseling between visits during the first year of intervention. Telephone dietary counseling once a year during the maintenance period of intervention	No dietary intervention, only general dietary advice as part of the standard care
Discount-card	A discount card with 25% discount on all fresh vegetables, fruit, berries and fish and several healthy foods available during the first year of intervention	
Delivery of free foods items	Delivery of free healthy food items at every visit at study center during the first 12 months of intervention. Delivery of a box with free food items to their homes two times during the first 12 months of intervention	
Cooking course	A one-day cooking course arranged by registered dietitians following a protocol in accordance with the NFBDG	
CRC-NORDIET webpage	A log-in restricted dynamic webpage containing extensive information regarding the NFBDG, dietary advice, recipes, week menus and portion sizes. The webpage is available to the end of study and it is continuously updated with new recipes in accordance to the NFBDG	
Inspiration days	The first inspiration day will contain: - Lectures about the NORDIET study - Diet: practical demonstrations of foods (fruits, vegetables, whole-grain products) and portion sizes according to the NFBDG performed by registered clinical dietitians - Physical activity: Lecture and practical demonstration by the physical therapists of home-based exercises to incorporate in daily life The patients are invited to inspiration group meetings every year after the first year of intervention. The group meetings will particularly focus on foods dampening oxidative stress and inflammation, and to encourage the patients to continue following the NFBDG. The physical activity section will consist of different topics at each meeting.	The first inspiration day will contain: - Lectures about the NORDIET study - Physical activity: Lecture and practical demonstration by the physical therapists of home-based exercises to incorporate in daily life
Physical exercise	All the participants are offered free access to exercise facilities at "Pusterommet" (http://pusterommene.no/) during the first year of intervention. They also get individual counseling by a physiotherapist	

*NFBDG: Norwegian food-based dietary guidelines

Additional file 2. Summary of the 13 recommendations of the Norwegian food-based dietary guidelines (NFBDG) (translated from the NFBDG)

	Recommendation	Explanations to the recommendations
1	A primarily plant-based diet is recommended, including plenty of vegetables, fruit, berries, wholegrain and fish, and limited quantities of red and processed meat, salt, added sugar and energy-rich foods	• A varied diet is the best way to achieve favourable health effects and an optimum intake of nutrients. • Choose mainly foods that contain limited quantities of fat, sugar and salt. • Choose foods that help to ensure an adequate intake of nutrients.
2	It is recommended to maintain a balance between energy intake and energy expenditure	• Energy intake from foods and drinks and energy consumption through physical activity, should be balanced, so that weight is maintained within the normal range. • Regular physical activity helps to maintain the energy balance. A large proportion of the population is overweight. For the overweight, weight loss should combine more physical activity with an energy-reduced diet. • The consumption of foods with high energy content should be limited. • The consumption of drinks with added sugar, such as carbonated drinks should be limited. • Within each food group, it is recommended to choose products that have the Keyhole label
3	Eat at least five portions of vegetables, fruit and berries every day	• It is recommended to eat at least five portions, corresponding to at least 500 grams altogether, of vegetables, fruit and berries every day. • About half of this intake should be in the form of vegetables and about half fruit and berries. • A portion corresponds to about 100 grams, for example as mixed salad, carrot, broccoli or cauliflower as an accompaniment to a main meal, a medium sized piece of fruit (apple, pear or orange) or a small bowl of berries. As a maximum, one glass of juice can be included as one portion. • The recommendation is to eat a variety of vegetables, fruit and berries of different colours, and include tomatoes and vegetables in the onion family in the diet. • Fresh, tinned, frozen, raw and cooked vegetables, fruit and berries can all be included. Dried fruit can also be included, but the portion size should be adjusted downward, and products with no added sugar should be chosen. • It is recommended to consume a moderate amount of nuts (about 140 grams per week). The nuts should be unsalted. The nuts are in addition to the recommended five portions of vegetables, fruit and berries. Nuts have high energy content and a high intake can promote weight increase. • Potatoes are not included in the recommended five portions of vegetables, fruit and berries. Potatoes are however an important food in the Norwegian diet and can certainly be included in a varied diet. Potatoes have a higher content of dietary fibre and more vitamins and minerals per energy unit that ordinary rice or pasta. Choose boiled or baked potatoes rather than chips, crisps and other potato products with added fat and sugar. • Pulses, seeds, spices and herbs are not included in the recommended five portions of vegetables, fruit and berries. These foods do however often have a high nutrient content and can certainly be included in a varied diet.

4	Eat at least four portions of wholegrain products every day	• Four portions of wholegrain products corresponds to about 70-90 grams of wholegrain per day (75 g of wholegrain per 10 MJ (2.400 kcal)). • Three slices of wholemeal bread or a large portion of wholemeal pasta or brown rice all correspond to about 75 grams of wholegrain. Breakfast cereals, porridge and crisp bread made with wholegrain are also good wholegrain sources. • At least half of the total consumption of grain products should be in the form of wholegrain. • Preferably, choose grain products with a high fibre content and low content of sugar, fat and salt, such as Keyhole-labelled products and wholemeal breads • Limit the consumption of grain products with a high content of fat, salt and sugar, such as a number of types of cakes, cereals, pizza and snacks.
5	Eat the equivalent of two or three portions of fish per week	• Weekly consumption of about 300-450 grams of fish is recommended. This corresponds to two or three main meal portions per week. • Alternatively, fish as a main meal can be replaced with fish as a sandwich topping. Six sandwich topping portions of fish approximately correspond to one main meal portion. • Both fatty and lean fish can be included, but it is recommended that at least 200 grams of the intake should be of fatty fish. • Preferably, choose Keyhole-labelled fish products
6	Low-fat dairy products should be included in your daily diet	• The daily consumption of low-fat dairy products is important for most people in order to ensure an adequate intake of certain nutrients, including calcium and iodine. Low-fat dairy products should therefore be included in the diet. • The consumption of dairy products that contain high levels of saturated fat and/or a high energy content (i.e. more than 950-1,150 kJ or 225-275 kcal per 100 grams), such as full-cream milk, cream, fatty cheese and butter, should be limited. This advice must be seen in context with the other dietary recommendations, so as to ensure a good fat quality in the complete diet. • Preferably, choose Keyhole-labelled dairy products.
7	It is recommended to eat lean meat and lean meat products, and limit the intake of red meat and processed meat	• Lean meat products are important for most people in order to ensure an adequate consumption of a number of nutrients. Moderate consumption of lean meat products can therefore be included in the diet. • This advice must be seen in context with the other dietary recommendations, so as to ensure a good fat quality in the complete diet. • Choose meat and meat products with a low fat and salt content. Preference should be given to the consumption of unprocessed meat. • Limit the consumption of red meat (beef, pork, lamb and goat) to 500 grams per week. This corresponds to two main meals with red meat and a limited amount as sandwich topping a week. When reducing the consumption of red meat, preference should be given to cutting the consumption of processed red meat. • Those with a high consumption of red meat could preferably replace some of this with white meat and fish. • Consumption of processed meat products (smoked, salted or preserved with nitrate or nitrite) should be limited. • Choosing Keyhole-labelled meat and meat products is recommended.

8	It is recommended to use cooking oil, liquid margarine or soft margarine	• Cooking oils and margarine with a low content of saturated fatty acids and a high content of unsaturated fatty acids, such as plant oils (e.g. rapeseed, sunflower, olive and soya oils) and liquid or soft margarine, should be used in preference to similar products with a great proportion of saturated fatty acids (such as those that contain a high percentage of palm oil) and low proportion of unsaturated fatty acid. • Limit the use of butter and butter-margarine blends because these have a high content of saturated fatty acids and a low content of polyunsaturated fatty acids. Butter and animal fats also may contain trans fatty acids and cholesterol. • The consumption of foods with high energy content should be limited. Cooking oils and soft or liquid margarine have high energy content, but also contribute with polyunsaturated fatty acids and fat soluble vitamins, and should therefore be included in the diet. • This advice must be seen in context with the other dietary recommendations, so as to ensure a good fat quality in the complete diet.
9	Water is recommended as the primary choice of drinks	• It is recommended that water makes up the major part of the fluid requirement. This includes tap water and bottled and mineral water (only normal mineral water not sweetened and carbonated soft drinks). • Tap water and most types of mineral water contain insignificant amounts of sodium (salt), but some types of mineral water can contain significant amounts of sodium (see Recommendation 11). • Skimmed milk and extra low-fat milk can certainly be included as a drink in the diet, so as to ensure an adequate intake of calcium and iodine (see Recommendation 6). • Consumption of alcohol is not recommended. • The consumption of drinks with added sugar, such as carbonated drinks should be limited (see Recommendations 2 and 10). • Fruit juice may be included as part of the recommendation for fruit, berries and vegetables (see Recommendation 3). High consumption of fruit juice should however be avoided. • Consumption of acidic (low pH) drinks, such as carbonated drinks with sugar or artificial sweeteners, and juice should be limited outside from mealtimes.
10	Limit your intake of added sugar	• It is recommended that the intake of added sugar should be limited to less than 10% of the total energy intake. • It is recommended to reduce the consumption of carbonated drinks, soft drinks, nectar, sweet biscuits, cakes and sweets. • The consumption of drinks with added sugar should be limited (see Recommendations 2 and 9).
11	Limit your intake of salt	• It is recommended to limit the intake of salt (sodium chloride) to a maximum of 6 grams per day (which corresponds to 2.4 grams of sodium). • Preferably, choose food with a low salt content. If food products state salt content, choose products with a low salt content or those with the Keyhole label. • Limit the consumption of food products with a high salt content. Industrial and processed food products contribute 70-80% of salt consumption for most people. Non-processed food contains far less salt than most processed food products. • Limit the use of table salt and salt in the preparation of food. Use other flavourings such as herbs and salt-free spices instead of salt. • Limit the consumption of mineral water with high levels of sodium or a high salt content. Tap water contains insignificant amounts, while mineral water may contain a considerable amount (1 gram of salt per litre, i.e. 0.4 grams of sodium per litre).

12	Dietary supplements may be necessary to ensure an adequate intake of nutrients for some groups in the population	• Dietary supplements are unnecessary for most people if they have a varied and healthy diet. • If a deficiency of a nutrient is clinically documented, a dietary supplement may be a good alternative if a corresponding intake from foods is difficult. This applies for example to iron deficiency, which is not uncommon among women. Iron supplements are not recommended as a general preventive measure, only if iron deficiency anaemia or low iron status has been documented. • Persons who do not eat fatty fish or who have an intake lower than the recommended lower limit (i.e. 200 grams per week) should take a daily supplement of cod liver oil or other omega-3 supplements, so as to ensure an adequate intake of long-chain polyunsaturated omega-3 fatty acids (EPA, DHA). The primary advice however is to eat fatty fish (see Recommendation 5). • Persons who do not have a sufficient intake of vitamin D should take cod liver oil or another vitamin D supplement daily during the period of the year with little exposure to the sun. Elderly people who spend little time out in the sunlight should take cod liver oil or another supplement with 10 micrograms of vitamin D per day in addition to regular dietary consumption. This also applies to persons with dark skin and others with too low exposure to sunlight. • Persons with a low energy intake (6.5-8 MJ/day or 1.550-1.900 kcal/d), should consider taking a multivitamin and mineral supplement in addition to their regular diet. • Persons with a very low energy intake (less than 6.5 MJ/d or 1.550 kcal/d) should always take a multivitamin and mineral supplement in addition to the regular diet. This applies especially to elderly people with low dietary intakes. • Women of childbearing age are recommended to take a supplement containing 400 micrograms of folate every day for a month before anticipated conception and for the first two or three months of pregnancy. • Care is advised when taking several supplements that contain the same nutrient, since a high intake could have a damaging effect.
13	It is recommended that everyone participates in least 30 minutes of physical activity per day	• Spend at least 30 minutes a day in moderate physical activity, corresponding to at least a brisk walk. If your general condition allows, this can be increased to an hour or more every day. Generally speaking, any form of physical exercise is better than none. • The time spent in physical activity can be divided into periods during the course of the day. • Physical activity is favourable for weight reduction and for prevention of weight increase after weight reduction. To maintain a large weight loss, 60 to 90 minutes of moderate physical activity most days a week is recommended.

Additional file 3. Detailed list of foods and drinks with high content of redox-active compounds and/or antioxidative effects

The following foods and drinks have high content of redox-active compounds and/or may have antioxidative effects individually or in combination in vitro models, animal models, clinical trials and/or epidemiological studies: coffee [1-8], green tea [2-4, 6, 9-11], black tea [2-4, 6], onion [1, 12], broccoli [1, 6, 9-11], tomatoes [6, 9-11], red cabbage [2-4, 9-11], kale [9-11], Brussel sprouts [9-11], artichoke [2-4], curly kale [2-4], peppers/paprika [2-4], chili peppers [2-4], carrots [9-11], pomegranates [2-4, 9-11], garlic [6], kiwifruit [13, 14], apples [6, 9-11], orange [6, 9-11], grapes [2-4, 9-11], plums [2-4], cherries [9-11], walnuts [2-4, 6, 9-11], chestnuts [2-4], peanuts [2-4], hazel nuts [2-4], almonds [2-4], thyme [1-4, 9-11, 15], oregano [1-4, 9-11, 15], lemon balm [15], clove [2-4, 15], allspice [2-4, 15], peppermint [2-4, 15], sage [2-4, 15], turmeric [1], rosemary [1-4, 9-11, 15], saffron [2-4], estragon [2-4], elderberries [16], dog rose [1-4, 9-11], cinnamon [2-4, 6, 15], chokeberries [9-11], blueberries/bilberries [2-4, 6, 9-11, 16, 17], blackberries [2-4, 9-11, 16], cranberries [2-4, 9-11], strawberries [2-4, 9-11], raspberries [2-4, 9-11], crowberries [2-4], black currants [2-4], dark chocolate [1-4, 9-11], pecan nuts [2-4, 9-11], olive [2-4, 9-11] and barley [2-4].

Furthermore, we have also identified that the following foods and drinks may have anti-inflammatory effects individually or in combination in cell cultures, animal models, clinical trials and/or epidemiological studies: coffee [5, 18-22], tomatoes [18, 21], carrots [21], pomegranates [21], walnuts [21, 22], nuts [23], strawberries [21], blueberries/bilberries [24, 25], crowberries [21], blackberries [21], dog rose [14], whole grains [26], thyme [21, 22], oregano [21, 22], turmeric [21], clove [21], allspice [21] and rosemary [21].

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Additional file 4. Questionnaires, biological samplings and measurements

	Baseline	6 mths	12 mths	3 yrs	5 yrs	7 yrs	10 yrs	15 yrs
Demographic information	X	X	X	X	X	X	X	X
Assessment of dietary intake								
FFQ	X		X	X	X	X	X	X
Compliance questionnaire	X	X	X	X	X	X	X	X
Food records	X	X						
24-hr recall	X							
Assessment of physical activity and function								
PA monitor	X	X	X	X	X	X	X	X
Self-reported PA	X	X	X	X	X	X	X	X
6MWT	X	X	X	X	X	X	X	X
Sit-to-stand test	X	X	X	X	X	X	X	X
Hand grip strength	X	X	X	X	X	X	X	X
Assessment of nutritional status								
PG-SGA	X	X	X	X	X	X	X	X
Anthropometric measurements								
Body weight	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X
Waist and hip circumference	X	X	X	X	X	X	X	X
Body composition analysis								
BIA	X	X	X	X	X	X	X	X
DXA	X	X	X	X	X	X	X	X
CT*								
Blood pressure	X	X	X	X	X	X	X	X
Biological samples								
Venous blood samples	X	X	X	X	X	X	X	X
Buffy coats from EDTA	X	X	X	X	X	X	X	X
Dried blood spot samples	X	X	X	X	X	X	X	X
Urine samples				X		X		X
Feces samples				X		X		X
Tumor tissue**	X							
Oral glucose tolerance test	X	X	X	X	X	X	X	X
Health status								
Quality of life	X	X	X	X	X	X	X	X
Fatigue	X	X	X	X	X	X	X	X

*CT images are routinely taken for clinical purposes pre-surgery and 5 and 10 years after surgery.
**Tumor tissue will be collected at surgery

FFQ: Food frequency questionnaire; 6MWT: 6 minutes walking test; BIA: bioelectrical impedance analysis; CT: computerized tomography; DXA: dual-energy x-ray absorptiometry; EDTA: ethylenediaminetetraacetic acid; PG-SGA: Patient-Generated Subjective Global Assessment; PA: physical activity

II

food & nutrition research

ORIGINAL ARTICLE

Relative validity of a short food frequency questionnaire assessing adherence to the Norwegian dietary guidelines among colorectal cancer patients

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Abstract

Background: The Norwegian food-based dietary guidelines (FBDG) aim at reducing the risk of developing chronic diseases and promote overall health. We studied the effect of the Norwegian FBDG in colorectal cancer (CRC) patients. There is a need for a time-efficient dietary assessment tool measuring adherence to these guidelines in patients treated for dietary dependent cancer, such as CRC patients.

Objective: To evaluate a new short food frequency questionnaire (NORDIET-FFQ), developed to estimate adherence to the Norwegian FBDG among CRC patients.

Design: Eighty-one CRC patients from both study groups in the Norwegian Dietary Guidelines and Colorectal Cancer Survival study, an ongoing dietary intervention, completed both the short 63-item NORDIET-FFQ and a 7-day weighed food record.

Results: The NORDIET-FFQ was on group level able to estimate intakes of fruits, vegetables, unsalted nuts, fish, fatty fish, high fat dairy products, unprocessed meat, processed meat, red meat, water, sugar-rich beverages, alcoholic drinks, and sugar- and fat-rich foods. Ranking of individuals according to intake was good (r = 0.31–0.74) for fruits and vegetables, fruits, unsalted nuts, whole grain products, sugar-rich cereals, fish, fatty fish, dairy products, red meat, water, sugar-rich beverages, alcoholic beverages, and sugar- and fat-rich foods. The NORDIET-FFQ was able to identify the individuals who did not fulfil the recommendations of fruits, vegetables, unsalted nuts, whole grains, low-fat dairy products, processed meat, water, alcoholic beverages, and sugar- and fat-rich foods (sensitivity: 67–93%).

Conclusions: The NORDIET-FFQ showed good ability in to estimate intakes of plant-based foods, fish, dairy products, meat, and energy-dense foods; adequate ranking of individuals according to intake of most recommendations except for unprocessed meat, processed meat, and vegetables; and importantly a good ability to identify those patients in need of dietary counselling for foods that are known to modulate the risk of CRC.

Trial registration: National Institutes of Health ClinicalTrials.gov; Identifier: NCT01570010.

Keywords: *dietary assessment tool; weighed food records; validity; dietary intake; food based dietary guidelines; cancer*

To access the supplementary material to this article, please see Supplementary files under 'Article Tools'.

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Most countries develop national food-based dietary guidelines (FBDG) (1–4). In 2011, the health authorities in Norway published updated FBDG, encouraging intake of a plant based diet with ample amounts of vegetables, fruits, berries, whole grains, and fish and limited amounts of red and processed meat, salt, sugar, alcohol, and high-energy foods. The Norwegian FBDG are similar to the national FBDG in most other developed countries (3, 5). A major aim of the Norwegian FBDG is to reduce risk of lifestyle related diseases such as cancer, cardiovascular diseases, diabetes, and obesity.

Colorectal cancer (CRC) is the third most common cancer in Norway and second most common cause of cancer death (6). Low intake of whole grains, foods containing dietary fibre, dairy products and high intake of red and processed meat, alcoholic drinks as well as increased body fat have been associated with higher risk of developing CRC (4). All of these risk factors are included in the Norwegian FBDG, but the national guidelines have a much broader perspective than only these risk factors related to CRC.

Little is known about the effect of diet on disease outcomes and survival in CRC patients. We have therefore initiated a large, long-term randomised controlled trial (RCT) (CRC-NORDIET) to study the effect of diet in CRC patients post-surgery (7). Instead of only focusing on the dietary factors associated with risk of CRC, participants in the CRC-NORDIET study are instructed to follow a dietary pattern that is consistent with the Norwegian FBDG, since CRC patients have increased risk of lifestyle-related co- and multimorbidities.

It is therefore of interest to assess to what extent CRC patients in the CRC-NORDIET study comply with the Norwegian FBDG, both those foods that are causally related to CRC as well as those foods that are related to other lifestyle-related co-and multimorbidities.

Dietary intervention studies as well as nutrition education and counselling would benefit from a user friendly, short dietary assessment tool. In nutritional research, a variety of comprehensive dietary assessment tools are used, including food frequency questionnaires (FFQs), 24-h dietary recall, and food records (8). The FFQ is an established assessment method often used when investigating the effects of diet on disease outcomes in populations or groups of dietary interventions (9, 10). Since most FFQs aim at capturing total habitual diet and therefore often include 200–300 questions, they are time-consuming for the respondents to complete, and data handling may be complex for the researcher (8, 11–17). Short FFQs are less time-consuming for both the patient and the researcher. Short FFQs designed to cover a recent time period (i.e. 1–2 months) have been shown to be useful for identifying dietary changes in individuals and in intervention studies (13, 17–20) and may also be applicable to dietary counselling of patients in a clinical setting (11).

In recent years, a number of short FFQs have been developed to monitor adherence to food recommendations (11, 21–27); however, none of these assess adherence to a national FBDG. As part of the ongoing CRC-NORDIET study (7), we developed a short semi-quantitative FFQ (NORDIET-FFQ), designed to estimate the adherence to the Norwegian FBDG. The objective of the present study was to validate the ability of the NORDIET-FFQ to assess adherence to the Norwegian FBDG in CRC patients.

Methods

Subjects and study design

Men and women aged 50–80 years old, with non-metastatic CRC (International classification of diseases (ICD)-10 18–20), staged I–III according to the TNM (tumour node metastases) staging system (28), and participating in the CRC-NORDIET study (7) were invited to take part in the present validation study. The participants in the validation study were recruited from both intervention (n = 48) and control groups (n = 33) at the follow-up visit 6 months after baseline of the study, from January 2014 to October 2015. About 15% of the participants received chemotherapy post-surgery, of which the mean time from last chemotherapy injection to the validation study start was 155 days. Hence, none of the participants included in the validation study underwent adjuvant treatment during the time frame covered by the dietary assessment tools. All seasons during a year were included. The participants completed the self-administered NORDIET-FFQ at the study centre and received a digital scale and weighed record (WR), to be completed at home within 2 weeks (Fig. 1).

Ethics and approvals

The CRC-NORDIET study is being carried out in accordance with the Helsinki Declaration and informed consent was obtained from all participants. The study was approved by the Regional Committees for Medical and Health Research Ethics (REC Protocol Approval 2011/836) and by the data protection officials at Oslo University Hospital, Oslo, Norway and Akershus University Hospital, Lørenskog, Norway. The study is registered on the National Institutes of Health ClinicalTrials.gov (Identifier: NCT01570010).

Characteristics of the participants

Anthropometric measurements (weight, height, and hip- and waist circumference) were measured as previously described (7). Level of education, smoking status, and tumour location were retrieved from other questionnaires within the clinical trial and from medical records.

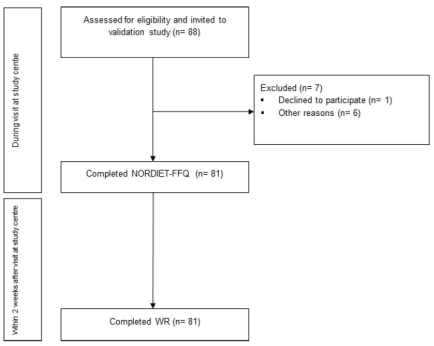

Fig. 1. Study design and timeline of the validation study.

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NORDIET-FFQ

The NORDIET-FFQ is a short semi-quantitative 63-item FFQ designed to assess dietary intake (in grams per day) over the previous 1–2 months. It takes on average 15 min to complete. The questions in the NORDIET-FFQ correspond to the food groups relevant for the Norwegian FBDG (3). The NORDIET-FFQ is not designed for estimation of total energy or nutrient intake.

The NORDIET-FFQ included questions of both frequency (how often the food item was consumed) and amount of the food items. The 63 questions cover the following food groups: fruit, berries, nuts, vegetables, cereals, beverages, cakes, sweet candy, breads and spreads, oils, margarine and butter, dairy products, fish, meat, rice, pasta, and dietary supplements. The questionnaires were checked for completeness by the researchers, so that incomplete answers could be corrected. Data from the NORDIET-FFQ were scanned and the image files transformed into data files using Cardiff Teleform 2006 Software (6.0) (Datascan, Oslo, Norway). The software proofread the answers in the NORDIET-FFQ pending approval by the handler. When values were missing the following rules were used: (1) when frequency was reported but amount was missing, the lowest amount was registered; (2) when amount was reported but the frequency was missing, the lowest frequency above 0 was registered; (3) when both frequency and amount were missing, they remained as missing values; (4) if the amount of food was reported and the frequency was reported as zero, the amount was removed.

The food composition database and nutrient calculation system developed at the Department of Nutrition, University of Oslo (KBS, version 4.7, 2010, AE-10), was used for the calculations of food and beverage intake (29).

Seven-day weighed food record

All participants were provided with a WR and a digital scale (5 kg kitchen scale, Clas Ohlson Model CFC2025, Oslo, Norway) and were instructed how to weigh and record all foods and beverages consumed during a period of 7 consecutive days. The participants returned the completed WRs to the study centre at Department of Nutrition, University of Oslo, by postal mail. Dietary data were retrieved from the WR and manually coded and imported into the food database AE-10 and KBS software system (KBS, 2010). The manual coding and import of data were done by two researchers (HBH and SFØ), in accordance with a protocol developed at the Department of Nutrition, University of Oslo. All of the 81 WRs were included in the analyses.

Dietary recommendations

Quantitative Norwegian FBDG

The questions about food and beverage intake in the NORDIET-FFQ were grouped according to the quantitative recommendations of the Norwegian FBDG as defined in Table 1. The main recommendations are listed in Table 1 together with the quantitative limits required to fulfil the Norwegian FBDG. The last two columns of Table 1 list all the specific questions in the NORDIET-FFQ that are included in calculation of adherence to the recommendations. Whole grain intake was estimated from whole grain products using a whole grain factor (30, 31). The lower range of recommended fish intake was used in the definition of daily intake (i.e. 300 g/week or 43 g/d).

The translation of qualitative Norwegian FBDG into quantitative limits

In order to measure adherence to the qualitative recommendations of the Norwegian FBDG we had to translate these qualitative recommendations into quantitative values and lower limits of intake (Table 2). The quantitative values used in the present paper are listed in the footnotes of Table 2. The last two columns of Table 2 list all the specific questions in the NORDIET-FFQ that are included in calculating adherence to the recommendations. Qualitative recommendations that included the terms 'limit' or 'reduce' were quantitatively defined as the highest acceptable amount of daily intake. For example, the recommendation regarding processed meat reads, 'Limit the intake of processed meat'. In this case we *a priori* set the quantitative limit required to fulfil the Norwegian FBDG to ≤20 g/d. This is equivalent to a fast-food meal or dinner with processed meat once a week. Moreover, the term 'preference' included in the recommendation of unprocessed meat (i.e. 'Preference should be given to the consumption of unprocessed meat') was defined as meaning that intake of unprocessed meat should exceed the intake of processed meat.

For recommendations where a daily intake of specific food items was specified, this was defined as the minimum amount that should be consumed daily with some modifications. For example, a moderate intake of unsalted nuts (about 140 g/week or 20 g/d) is recommended. However, because nuts are protein and energy dense, high intakes may lead to weight gain. Therefore, the recommendation of unsalted nuts was defined as a daily intake of at least 20 g or more among normal weight [body mass index (BMI) < 25] individuals and between 20 and 30 g/d among overweight and obese individuals (BMI ≥ 25). In the case of dairy products, the recommendation states that 'Low-fat dairy products should be included in your daily diet'. The recommended daily amount was defined as at least half a portion of low-fat dairy products per day. Water is recommended as the primary choice of beverage; however, there is no quantitative daily recommendation of water intake in the Norwegian FBDG. Therefore, we determined that, to fulfil this recommendation, at least 25% of the daily beverage intake should be water.

Table 1. The quantitative NFBDG and corresponding questions in the NORDIET-FFQ

Quantitative NFBDG	Intake required to fulfil NFBDG	Foods and drinks included to calculate dietary intake (g/d)
1.1 It is recommended to eat at least five portions, corresponding to at least 500 g altogether, of vegetables, fruit and berries every day.[a]	≥500 g/d	Large fruits (e.g. apple, nectarine, banana, orange) Medium fruits (e.g. clementine, kiwifruit, plum) Small fruits (e.g. grapes) Berries (frozen or fresh strawberries, bilberries, raspberries, etc.) Dried fruits (e.g. raisins, apricot, prunes, dried apples) Fresh fruits and vegetables used as spread on bread[b] Garlic Onion and leek Tomatoes Tomato sauce Mixed salad Vegetables (e.g. carrots, broccoli, cauliflower) Juice [1 glass of juice (2 dL) counts as one portion of fruit (=100 g); intake >1 glass does not count]
1.2 About half of this intake should be in the form of fruit and berries.	≥250 g/d	Large fruits (e.g. a whole apple, nectarine, banana, orange) Medium fruits (e.g. clementine, kiwifruit, plum) Small fruits (e.g. grapes) Berries (frozen or fresh strawberries, bilberries, raspberries, etc.) Dried fruits (e.g. raisins, apricot, prunes, dried apples) Fresh fruits used as spread on bread (50% of subquestion 9g)[b] Juice [1 glass juice (2 dL) counts as 1 portion of fruit (=100 g); intake >1 glass does not count]
1.3 About half of this intake should be in the form of vegetables.[a]	≥250 g/d	Vegetables (e.g. carrots, broccoli, cauliflower) Fresh vegetables used as spread on bread (calculated as 50% of subquestion 9g in the NORDIET-FFQ)[b] Tomatoes Tomato sauce Mixed salad Garlic Onion and leek
2.1 Eat at least four portions of whole grain products every day. Four portions of whole grain products corresponds to about 70–90 g of whole grains per day.[c,d]	Women: ≥70 g/d Men: ≥90 g/d	Bread with 25–50% wholemeal flour (60% cereals) Bread with 50–75% wholemeal flour (60% cereals) Bread with 75–100% wholemeal flour (60% cereals) Wholemeal crisp bread Sweetened cereals (e.g. Corn Flakes) Unsweetened cereals (e.g. oatmeal porridge) Brown riceWhole grain pasta
2.2 At least half of the total consumption of grain products should be in the form of whole grains.[c,d]	Whole grain (g/d) > 50% of total grains (g/d)	Bread with 0–25% wholemeal flour (60% cereals) Bread with 25–50% wholemeal flour (60% cereals) Bread with 50–75% wholemeal flour (60% cereals) Bread with 75–100% wholemeal flour (60% cereals) White crisp bread Wholemeal crisp bread Sweetened cereals (e.g. Corn Flakes) Unsweetened cereals (e.g. oatmeal porridge) White rice Brown rice White pasta Whole grain pasta Cakes, buns, waffles, sweet biscuits
3.1 Weekly consumption of 300–450 g of fish is recommended.[e]	≥43 g/d (300 g/week)	Fatty fish (e.g. salmon, trout, herring, halibut) Lean fish (e.g. cod, pollock, angler) Processed fish (e.g. fish gratin, fish cakes) (40% fish) Fish as spread (e.g. mackerel, smoked salmon, herring)
3.2 It is recommended that at least 200 g of the intake should be of fatty fish.	≥29 g/d	Fatty fish (e.g. salmon, trout, herring, halibut) Fish as spread (e.g. mackerel, smoked salmon, herring)
4.1 Limit the consumption of red meat (beef, pork, lamb, and goat) to 500 g/week.	≤71 g/d	Unprocessed red meat Processed red meat Red meat as spread

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Table 1. Continued

Quantitative NFBDG	Intake required to fulfil NFBDG	Foods and drinks included to calculate dietary intake (g/d)
5.1 Cooking oils and margarine with a low content of saturated fatty acids and a high content of unsaturated fatty acids should be used in preference to similar products with a great proportion of saturated fatty acids.	Users of cooking oil, liquid margarine, or soft margarine and non-users of butter with high content of saturated fatty acids	Margarine, butter, and oil as spread Margarine, butter, and oil in cooking
6.1 Consumption of alcohol is not recommended.	0 g/d	Beer with alcohol Wine with alcohol Liquor

NFBDG, Norwegian food-based dietary guidelines; NORDIET-FFQ, NORDIET food frequency questionnaire
[a]Not including legumes or potatoes.
[b]Jam not included.
[c]Not including sausage rolls, tortillas, hamburger bread, pizza dough, etc.
[d]Whole grain factor used in calculation of intake of whole grains from whole grain products (bread contains 60% flour):

- Bread with 0–25% wholemeal flour: (60*0)/10,000 = 0
- Bread with 25–50% wholemeal flour: (60*25)/10,000 = 0.15
- Bread with 50–75% wholemeal flour: (60*50)/10,000 = 0.30
- Bread with 75–100% wholemeal flour: (60*75)/10,000 = 0.45
- Crisp bread = 0
- Whole grain crisp bread = 1
- Sweetened cereals = 0.25
- Unsweetened cereals = 0.75

Boiled rice and pasta contain 70% water and 30% cereal. Whole grain factor used in calculation of whole grain intake from rice and pasta:

- Brown rice = 0.30
- White rice = 0
- Whole grain pasta = 0.30
- White pasta = 0

[e] Not including shellfish, mussels, or roe.

Table 2. The qualitative NFBDG defined as quantitative recommendations and corresponding questions in the NORDIET-FFQ

Qualitative NFBDG	Intake required to fulfil the dietary recommendations.(See footnotes for estimation of quantitative limits when the recommendations are not explicit.)	Foods and drinks included to calculate dietary intake (g/d)
1.1 It is recommended to consume a moderate amount of unsalted nuts (about 140 g/week).[a]	≥20 g/d nuts and BMI < 25[b] 20 g/d ≤ nuts < 30 g/d and BMI ≥ 25[c]	Unsalted nuts (e.g. almonds, peanuts, walnuts)
2.1 Reduce cereals with high content of fat and sugar.[d]	<20 g/d[e]	Sweetened cereals (e.g. Corn Flakes) Cakes, buns, waffles, sweet biscuits
3.1 Low-fat dairy products should be included in your daily diet.[d,f,g]	≥100 g/d[h]	Low-fat dairy products Reduced-fat cheese lean milk
3.2 The consumption of dairy products that contain high levels of saturated fat and/or a high energy content should be limited.[i,j,k]	<20 g/d[l]	High-fat dairy products High-fat cheese Whole milk
4.1 Moderate consumption of unprocessed meat can be included in the diet	≥20 g/d[m]	Unprocessed red meat Unprocessed white meat
4.2 Preference should be given to the consumption of unprocessed meat.	Unprocessed meat (g/d) >50% of total meat (g/d)	Unprocessed red meat Processed red meat Unprocessed white meat Processed white meat Red meat as spread White meat as spread

Table 2. Continued

Qualitative NFBDG	Intake required to fulfil the dietary recommendations.(See footnotes for estimation of quantitative limits when the recommendations are not explicit.)	Foods and drinks included to calculate dietary intake (g/d)
4.3 Limit the intake of processed meat.	≤20 g/d[n]	Processed red meat Processed white meat Red meat as spread White meat as spread
5.1 Water is recommended as the primary choice of drink.	Water (g/d) ≥25% of total drinks (g/d)	Water (e.g. tap or bottled water) Beer with alcohol Wine with alcohol Liquor Beverages without added sugar (e.g. mineral water, light soft drinks) Juice (e.g. apple juice, orange juice, etc.) Beverages with added sugar (e.g. soft drinks, nectar, etc.) Lean milk Whole milk Filtered coffee
5.2 The consumption of drinks with added sugar, such as carbonated drinks, should be limited.	≤20 g/d[o]	Other coffee Tea Sugar-rich beverages
6.1 Reduce intake of foods with high content of sugar and fat.	≤20 g/d[p]	Cakes, buns, waffles, sweet biscuits Dessert Chocolate, sweet candy Chips Sugar-rich spreads (e.g. honey, jam, peanut butter, etc.)

NFBDG, Norwegian food-based dietary guidelines; NORDIET-FFQ, NORDIET food frequency questionnaire.
[a]Salted nuts not included. Upper limit of the range of acceptable intake is based on the proportion of energy (about 7%) contribution of nuts to total energy intake: 30 g nuts contain about 180 kcal.
[b]Intake of at least 20 g/d unsalted nuts if normal weight (BMI < 25).
[c]Intake of nuts between 20 and 30 g/d if overweight (BMI ≥ 25).
[d]Lean milk with less than 1.5% fat.
[e]Acceptable amount of intake equal to one portion per week.
[f]Defined as dairy products (not cheese and milk) containing less than 20% fat and dairy products labelled as light or reduced fat or containing less than 950–1,150 kJb energy.
[g]Defined as cheese containing less than 17% fat, cheese labelled as light or reduced fat, or containing less than 950–1,150 kJ energy.
[h]Should include at least half portion per day (1 portion = 1 glass of lean milk = 200 g).
[i]Whole milk with more than 3.5% fat.
[j]Defined as dairy products (not cheese and milk) containing more than 20% fat and/or energy content more than 950–1,150 kJ.
[k]Defined as cheese containing more than 17% fat, cheese not labelled as light/reduced fat, or containing more than 950–1,150 kJ energy.
[l]Acceptable amount of intake equal to one portion per week.
[m]Moderate intake defined as at least one portion of unprocessed meat per week.
[n]Acceptable amount of intake equal to one portion per week.
[o]Acceptable amount of intake equal to one small portion per week.
[p]Acceptable amount of intake equal to one large portion per week.

Sample size

A sample size of 40 men and 40 women allows the detection of differences of one portion of fruit or vegetable (one portion = 100 g) between test and reference methods, assuming a standard deviation of 1.6 portion (or 160 g) (32, 33) with a significance level of 5% and power of 80%. Moreover, a sample size of 38 men and 38 women was needed to detect a correlation coefficient of 0.5 or higher, with a significance level of 5% and power of 90% (34).

Statistical analysis

Data were analysed using IBM SPSS Statistics, version 22. All *p*-values were two-sided with a significance level of 5%. All data were checked for normal distribution by evaluating histograms, normal Q–Q plots, and the Kolmogorov–Smirnov test ($p > 0.05$).

All subject characteristics were normally distributed and are presented as means with 95% confidence interval. The categorical data are presented as frequencies and

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percentages. Most of the estimates of food and beverage intakes were not normally distributed and therefore are presented as median, 5th, and 95th percentile. Depending on distribution, a Student's *t*-test or Mann-Whitney U test was used to compare two groups with regard to continuous variables. Categorical variables were compared by the Fischer exact test and Pearson chi-square test. Wilcoxon signed-rank test for paired data was used to check for difference in median intake between the two dietary methods (NORDIET-FFQ and WR).

Spearman's rank order correlation (rho) was calculated to explore the strength of the relationship between the continuous variables from the two different methods. We used the levels of agreement between two methods as defined by Hankin et al. (35), of which a correlation below 0.3 is poor, between 0.3 and 0.49 is fair, and above 0.5 is satisfactory. Kappa correlation was used to explore the strength of the relationship between the categorical variables of 'Oil, margarine, and butter' from the two different methods. Bland–Altman plots were used to explore bias such as over- or under-reporting (estimated by mean differences), limits of agreement (mean difference ± 1.96 SD), and presence of outliers in the data (36, 37).

To evaluate the participants' adherence to the dietary recommendations as described in Tables 1 and 2, we calculated the NORDIET-FFQs sensitivity and specificity compared with the WR. Sensitivity was defined as the percentage of subjects who reported not fulfilling the recommendations for both the NORDIET-FFQ and WR assessments divided by the number of patients not fulfilling the recommendations according to the WR only. Specificity was defined as the percentage of subjects who reported fulfilling the recommendations for both the NORDIET-FFQ and WR assessments divided by the number of subjects fulfilling the recommendations according to the WR only. Sensitivity and specificity above 60% was defined as good.

Results

Eighty-one participants accepted the invitation (92% participation rate, Fig. 1). General characteristics of the study population are presented in Table 3. Daily mean energy intakes estimated from the WR were 8.9 and 7.6 MJ for men and women, respectively.

Intakes of food and beverages from the NORDIET-FFQ and WR

Median intakes of food and beverages estimated from the NORDIET-FFQ and the WR are presented in Table 4. Overall, the NORDIET-FFQ was able to estimate intake of the main food groups in the Norwegian FBDG and that are associated with cancer risk, except for whole grain products, water, and red and processed meat. Correlation coefficients between intakes estimated from the NORDIET-FFQ and WR are presented in Table 5. Correlation coefficients ranged from 0.12 for unprocessed meat to 0.74 for

Table 3. Characteristics of the validation group, all participants in total and stratified by gender

Variables	Total (*n* = 81)	Men (*n* = 44)	Women (*n* = 37)	*p*
Age, years				
Mean (95% CI)	65.0 (63.4, 66.6)	65.4 (63.1, 67.7)	64.5 (62.1, 66.9)	0.59[a]
Smokers, *n* (%)	6 (7.4)	3 (6.8)	3 (8.1)	<1.0[b]
Energy intake, kJ[d]	8,362 (7,859, 8,865)	8,929 (8,215, 9,643)	7,640 (7,065, 8,214)	0.007[a]
Education, *n* (%)				
Primary school	5 (6.2)	3 (6.8)	2 (5.4)	0.035[b]
Lower secondary/high school	35 (43.2)	22 (50.0)	13 (31.5)	
College/university	41 (50.6)	19 (43.2)	22 (59.5)	
Anthropometry (mean, 95% CI)				
Weight, kg	78.26 (74.5, 82.1)	85.7 (81.9, 89.4)	70.0 (64.7, 75.3)	<0.001[a]
Height, m	1.73 (1.71, 1.75)	1.78 (1.76, 1.80)	1.67 (1.65, 1.68)	<0.001[a]
BMI, kg/m^2	26.1 (25.0, 27.2)	26.9 (25.8, 28.2)	25.1 (23.4, 26.9)	0.73[a]
Waist circumference, cm	93.8 (90.6, 97.1)	99.9 (96.9, 102.3)	87.0 (82.2, 91.9)	<0.001[a]
Hip circumference, cm	101.2 (98.9, 103.1)	101.2 (99.0, 103.3)	100.7 (96.9, 104.6)	0.84[a]
Tumour classification *n* (%) (total *n* = 73, men *n* = 38, women *n* = 35)				
TNM I	14 (19.2)	10 (26.3)	4 (11.4)	0.089[c]
TNM II	34 (46.6)	19 (50.0)	15 (42.9)	
TNM III	25 (34.2)	9 (23.7)	16 (45.7)	

TNM, tumour node metastases; BMI, body mass index.
[a]Student's *t*-test.
[b]Fischer exact test (two-sided).
[c]Pearson's chi-square test.
[d]Estimated energy intake from the 7-day weighed food records.

Table 4. Estimated intake of food groups according to Norwegian FBDG from NORDIET-FFQ and WR, all participants in total and stratified by gender

Food and beverages[a]	NORDIET-FFQ			WR			*p*[c]		
	Total (*n* = 81)	Men (*n* = 44)	Women (*n* = 37)	Total (*n* = 81)	Men (*n* = 44)	Women (*n* = 37)			
	Median (P_5, P_{95})[b]	Median (P_5, P_{95})[b]	Median (P_5, P_{95})[b]	Median (P_5, P_{95})[b]	Median (P_5, P_{95})[b]	Median (P_5, P_{95})[b]	P_{total}	P_{men}	P_{women}
Fruit, berries, and vegetables,[d] g/d	325 (155, 763)	292 (122, 677)	375 (186, 831)	353 (129, 744)	325 (125, 845)	380 (120, 781)	0.77	0.21	0.39
Fruit and berries,[d] g/d	173 (61, 450)	146 (40, 440)	181 (67, 530)	198 (23, 461)	188 (25, 469)	206 (0, 508)	0.38	0.89	0.26
Vegetables, g/d	144 (39, 396)	132 (27, 337)	155 (72, 478)	163 (59, 346)	151 (57, 371)	179 (70, 300)	0.17	0.06	0.98
Unsalted nuts, g/d	4 (0, 23)	2 (0, 23)	5 (0, 25)	0 (0, 26)	0 (0, 26)	1 (0, 26)	0.03	0.61	0.015
Whole grain products, g/d	87 (28, 197)	87(24, 223)	92 (35, 137)	44 (12, 128)	45.9 (6, 138)	44 (16, 116)	<0.001	<0.001	<0.001
Cereals with high content of fat and sugar	17 (0, 28)	13 (0, 65)	17 (0, 117)	28 (0, 105)	22 (0, 133)	32 (0, 88)	0.001	0.008	0.044
Fish, g/d	86 (22, 158)	85 (5, 187)	86 (30, 146)	82 (19, 167)	101 (16, 178)	77 (17, 170)	0.76	0.37	0.18
Fatty fish, g/d	41 (0, 84)	31 (0, 84)	42 (9, 84)	44 (0, 116)	50 (0, 129)	37 (0, 115)	0.01	0.35	0.012
Low-fat dairy products,[e] g/d	121 (0, 476)	130 (0, 563)	114 (0, 344)	151 (2, 626)	160 (0.5, 739)	147 (5, 400)	0.003	0.04	0.03
High-fat dairy products,[f] g/d	17 (0, 213)	17 (0, 203)	14 (0, 406)	32 (0, 145)	34 (1, 185)	29 (2, 159)	0.10	0.20	0.25
Unprocessed meat,[g] g/d	44 (0, 127)	44 (3, 131)	42 (0, 89)	47 (0, 118)	54 (1, 147)	46 (0, 117)	0.92	0.73	0.73
Red meat, g/d	47 (0, 129)	65 (0, 132)	42 (0, 103)	74 (0, 157)	95 (11, 215)	54 (0, 151)	<0.001	<0.001	0.06
Processed meat,[g] g/d	31 (1, 104)	43 (3, 134)	27 (0, 95)	43 (0, 120)	63 (5, 135)	29 (0, 65)	0.03	0.006	0.59
Water, g/d	274 (45, 1023)	274 (0, 959)	274 (0, 1151)	401 (0, 1624)	290 (0, 1443)	607 (39, 1834)	0.01	0.3	0.008
Sugar-rich beverages, g/d	0 (0, 166)	0 (0, 346)	0 (0, 86)	0 (0, 198)	0 (0, 234)	0 (0, 144)	0.09	0.47	0.09
Alcoholic drinks in total, g/d	98 (0, 651)	155 (0, 950)	64 (0, 205)	86 (0, 947)	120 (0, 1079)	70 (0, 298)	0.72	0.37	0.45
Sugar and fat rich foods, g/d	53 (0, 181)	52 (0, 199)	53 (3, 188)	70 (2, 174)	68 (1, 191)	77 (8, 175)	0.07	0.57	0.03

NORDIET-FFQ, NORDIET Food Frequency Questionnaire; WR, 7-day weighed food records

[a]Food groups defined in Tables 1 and 2.

[b]P_5 = 5th percentile, P_{95} = 95th percentile.

[c]Wilcoxon signed-rank test, *p*-values for median intake of food groups from NORDIET-FFQ and WR, total and between genders.

[d]Includes juice, defined as maximum 1 portion of fruit = 100 g.

[e]Includes low-fat dairy products (containing less than 20% fat), reduced-fat cheese (less than 17% fat), and lean milk (less than 1.5% fat).

[f]Includes high-fat dairy products (containing more than 20% fat), high-fat cheese (more than 17% fat), and whole milk (more than 3.5% fat).

[g]Total meat intake = unprocessed + processed meat.

alcoholic beverages. However, most food groups showed fair and satisfactory correlations, with the exception of poor correlations for unprocessed meat, processed meat, and vegetables. Bland–Altman analyses are presented in Fig. 2 and Supplementary file 3. The majority of the plots (i.e. differences between methods on the *y*-axis against the mean value of methods on the *x*-axis) were within the 95% limit of agreement for each food group. At the upper level of intake of foods, there was a wider scatter of difference. Sensitivity and specificity analyses are presented in Table 6. The NORDIET-FFQ was able to identify individuals in need of dietary counselling for most of the guidelines, with the exception of red meat, unprocessed meat, fish, and sugar-rich beverages. Estimated median intakes of the individual food items (ungrouped) are presented in Supplementary file 1, with associated correlations coefficients between test and reference method in Supplementary file 2.

Fruits, berries, vegetables, and nuts

Median intakes of the food groups 'Fruits, berries, and vegetables', 'Fruits and berries', and 'Vegetables' did not differ significantly between the methods, for all participants in total or when divided by gender (Table 4). However, the limits of agreement were wide and under-reporting increased at high intakes (Fig. 2a and b, Supplementary file 3A). The Spearman's rho was fair for the first two food groups, but poor for 'Vegetables' (Table 5). The questions about fruits and vegetables in the NORDIET-FFQ showed sensitivity in the range of 84–87% and a low specificity ranging from 14 to 50% (Table 6).

The median intake of unsalted nuts did not differ significantly between the NORDIET-FFQ and WR for men only. Moreover, with regard to differences between the two methods the limits of agreements were 20 g above and below the mean difference (Fig. 2c). Spearman's rho was satisfactory (Table 5), the sensitivity was good, and specificity was low (Table 6).

Whole grain products

There was significant difference in median intakes of whole grain products and cereals with high content of fat and sugar between the two methods but with satisfactory Spearman's rho (Tables 4 and 5). The NORDIET-FFQ tended to report higher intakes in the category of 'Whole grain products' on the group level, with almost half of the recommended daily intake, which increased with higher intakes in both women and men (Fig. 2d). However, the NORDIET-FFQ was able to identify individuals not fulfilling the dietary recommendation for whole grain products among men and women, respectively (Table 6).

Table 5. Spearman rank order correlation (*r*) of food and beverages groups between NORDIET-FFQ and WR, all participants in total and stratified by gender

Foods and beverages[a]	NORDIET-FFQ/WR, *r*		
	Total (*n* = 81)	Men (*n* = 44)	Women (*n* = 37)
Total fruit, berries, and vegetables[b]	0.41*	0.42*	0.33
Fruit and berries[b]	0.48*	0.49*	0.44*
Vegetables	0.15	0.11	0.15
Unsalted nuts	0.52*	0.58*	0.40
Whole grain products	0.55*	0.68*	0.28
Cereals with high content of fat and sugar	0.31*	0.23	0.40*
Fish	0.37*	0.51*	0.18
Fatty fish	0.35*	0.46*	0.14
Low-fat dairy products[c]	0.73*	0.78*	0.70*
High-fat dairy products[d]	0.46*	0.23	0.73*
Unprocessed meat	0.12	0.11	0.15
Red meat	0.45*	0.43*	0.39
Processed meat	0.29	0.23	0.24
Water	0.45*	0.40*	0.42*
Sugar-rich beverages	0.46*	0.64*	0.16
Alcoholic drinks in total	0.74*	0.78*	0.71*
Sugar- and fat-rich foods	0.49*	0.43*	0.61*

NORDIET-FFQ, NORDIET food frequency questionnaire; WR, 7-day weighed food record

[a]Food groups defined in Tables 1 and 2.

[b]Includes juice, defined as maximum 1 portion of fruit = 100 g.

[c]Includes low-fat dairy products (containing less than 20% fat), reduced-fat (less than 17% fat) and lean milk (less than 1.5% fat).

[d]Includes high-fat dairy products (containing more than 20% fat), high-fat cheese (more than 17% fat), and whole milk (more than 3.5% fat).

*Correlation is significant at the 0.01 level (two-tailed).

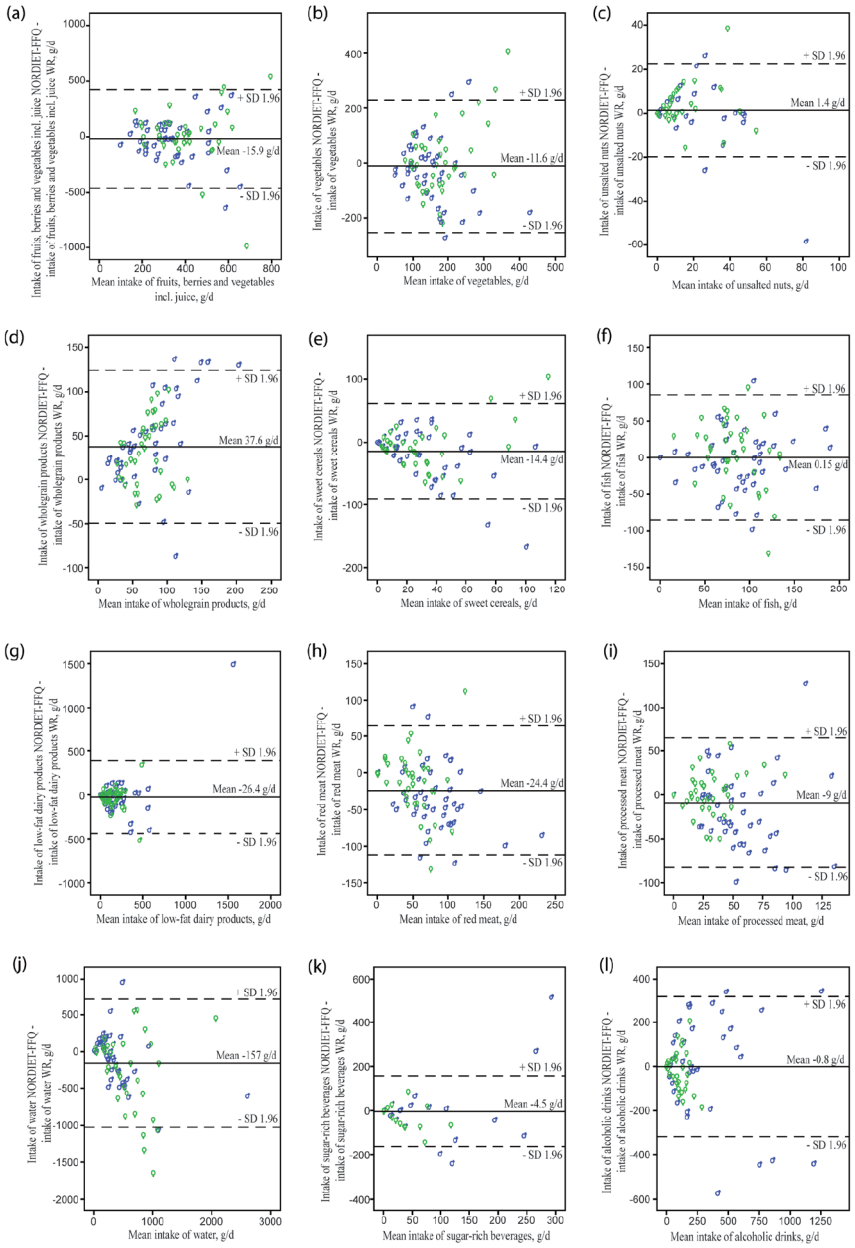

Fig. 2. Bland–Altman plots depicting the mean differences [NORDIET-FFQ minus weighed food dairy (WR)] for intake of food groups in grams per day: (a) fruits, berries, vegetables including juice; (b) vegetables; (c) unsalted nuts; (d) whole grain products; (e) sweet cereals; (f) fish; (g) low-fat dairy products; (h) red meat; (i) processed meat; (j) water; (k) sugar-rich beverages; (l) alcoholic drinks. The solid line represents the mean, and the dashed lines represent the 1.96 SDs of the observations. Females are denoted with the symbol ♀ the symboldwith the symbol ♂.

The under-reporting of intake of the category 'Cereals with high content of fat and sugar' showed a trend towards increasing differences between methods with higher intakes (Fig. 2e). The questionnaire was only able to identify individuals fulfilling the recommendations of 'At least half of the grains should be whole grains' and 'Reduce cereals with a high content of fat, salt, and sugar' (Table 6).

Fish

Median intakes of fish did not differ significantly between the two assessment methods on group level. Estimated intakes of fatty fish were significantly different for women but not for men (Table 4). The differences in intakes of fish and fatty fish between the methods did not show any trend in the distribution but were scattered above and below the

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Table 6. Sensitivity and specificity of the NORDIET-FFQ to detect participants not complying or complying with the Norwegian FBDG relative to WR

Guideline	Sensitivity *n*[a] (%)	Specificity *n*[b] (%)
1.1 Include vegetables, fruits, and berries in your daily diet.	57 (85.1)	3 (21.4)
1.2 About half of the intake should be as fruits and berries.	48 (84.2)	12 (50.0)
1.3 About half of the intake should be as vegetables.	58 (86.6)	2 (14.3)
1.4 A moderate amount of unsalted nuts should be included in your daily diet.	66 (93.0)	5 (55.6)
2.1:		
• Men should include at least 90 g of whole grains in their daily diet.	21 (66.7)	4 (55.3)
• Women should include at least 70 g of whole grains in their daily diet.	13 (100)	7 (43.3)
2.2 At least half of the grains should be whole grains.	5 (29.4)	62 (96.9)
2.3 Reduce cereals with high content of fat, salt, and sugar.	20 (41.7)	27 (81.8)
3.1 Include intake of fish in your diet.	5 (41.7)	64 (92.8)
3.2 Include fatty fish in your diet.	9 (34.6)	45 (81.8)
4.1 Low-fat dairy products should be included in your daily diet.	21 (80.8)	39 (70.9)
4.2 High-fat dairy products should be limited.	34 (57.6)	17 (77.3)
5.1 Include unprocessed meat in your usual diet.	1 (8.0)	61 (89.7)
5.2 Limit intake of red meat (beef, pork, lamb, goat).	16 (38.1)	32 (82.1)
5.3 Give preference to unprocessed meat over processed meat.	12 (38.7)	33 (66.0)
5.4 Reduce intake of processed meat.	51 (82.3)	7 (36.8)
6.1 It is recommended to use cooking oil, liquid margarine, or soft margarine more than butter with a high content of saturated fatty acids.	15 (46.9)	40 (81.6)
7.1 Water is recommended as the primary choice of drinks.	25 (73.5)	23 (48.9)
7.2 Reduce sugar-rich beverages.	14 (51.9)	48 (88.9)
7.3 No alcohol intake.	57 (96.6)	16 (72.7)
8.1 Reduce intake of foods with high content of sugar and fat.	63 (92.6)	8 (61.5)

Norwegian FBDG, Norwegian food-based dietary guidelines, NORDIET-FFQ, NORDIET food frequency questionnaire; WR, 7-day weighed food record.
[a]Subjects reported not fulfilling the recommendations for both the NORDIET-FFQ and WR.
[b]Subjects reported fulfilling the recommendations for both the NORDIET-FFQ and WR.

mean differences (Fig. 2f and Supplementary file 3B). The Spearman's rho was fair, sensitivity was low, and the specificity was high for both food groups (Tables 4 through 6).

Dairy products

The median intake of low-fat dairy products was significantly different between the two methods, but the Spearman's rho was satisfactory (Tables 4 and 5). The differences between the methods were evenly distributed above and below the mean difference, which showed a mean under-reporting of 26 g/d on the group level. The limits of agreement were mostly within the amount of two glasses of milk (Fig. 2). The median intake of high fat dairy products was not significantly different between the methods, and the Spearman's rho was fair for the total population, poor for men, and satisfactory for women (Tables 4 and 5). Both sensitivity and specificity were high for low fat dairy products, but the sensitivity was lower for high fat dairy products (Table 6).

Meat

The NORDIET-FFQ was able to estimate intakes of unprocessed meat, red meat (only women), and processed meat (only women) on the group level (Table 4). Moreover, red meat showed a fair Spearman's rho, whereas unprocessed meat and processed meat showed a poor Spearman's rho (Table 4). The limits of agreements were almost within 140 g (Fig. 2h and i, Supplementary file 3D). The NORDIET-FFQ was only able to identify individuals in need of dietary counselling for intakes of processed meat (Table 6). However, the NORDIET-FFQ was able to identify those who followed the recommendations for intakes of red meat and unprocessed meat (specificity, 90 and 82%) but not for processed meat (specificity of 37%) (Table 6).

Oil, margarine, and butter

The NORDIET-FFQ was able to identify participants who fulfilled the recommendations for intakes of dietary fat in their diets but not those who did not fulfil the recommendations (Table 6). Moreover, the measure of agreement between the methods was poor (kappa coefficient = 0.29, p <0.006).

Water and other beverages

Median intakes of water were significantly different for women and the total population and the Spearman's rho was fair (Tables 4 and 5). The underestimation of water from the NORDIET-FFQ increased with higher intakes

(Fig. 2j). Median intakes of beverages with added sugar were not significantly different between the methods and the Spearman's rho was fair for all participants in total, and satisfactory and poor among men and women, respectively (Tables 4 and 5, Fig. 2k). There were no significant difference between the methods in median intakes of alcoholic drinks in total and the Spearman's rho was satisfactory (Tables 4 and 5). The sensitivity analyses of beverages ranged from 52% ('Reduce sugar rich beverages') to 97% ('No alcoholic intake'), and the specificity ranged from 49% ('Water is recommended as the primary choice of drink') to 89% ('Reduce sugar-rich beverages') (Table 6).

Sugar- and fat-rich foods

The NORDIET-FFQ was able to estimate median intakes and to rank individual intakes of sugar- and fat-rich foods on the group level (Tables 4 and 5, Supplementary file 3E). The NORDIET-FFQ was also able to identify those not fulfilling the recommendation and moderately those who fulfilled the recommendation (Table 6).

Discussion

In the present study, we evaluated the NORDIET-FFQ's ability to assess adherence to the Norwegian FBDG in CRC patients. The NORDIET-FFQ was able to estimate intakes of the main dietary guidelines, such as fruits, vegetables, fish, meat, high-fat dairy products, beverages, and energy-dense foods. Only three food groups showed significant differences between methods for both genders, of which 'Low-fat dairy products' and 'Cereals with high content of sugar and fat' were under-reported and the 'Whole grain products' was over-reported in the NORDIET-FFQ compared to the WR. We speculate that the under-reporting of unhealthy cereals and the over-reporting of healthy whole grain products may be a result of social desirability bias, as seen in other studies, where presumed unhealthy foods are under-reported and healthy foods are over-reported (38–40). The underreporting of 'Low fat dairy products' may also be explained by participants having difficulty interpreting the dairy questions and not knowing if the dairy products they use are high- or low-fat products. There is a wide range of dairy products on the market with varying fat content and a valid intake estimate of this food category relies heavily on participants' knowledge of fat content in the products they consume. Thus, this may reduce the ability of the NORDIET-FFQ to estimate intakes of low-fat products. The estimate of the category 'Low fat dairy products' was an aggregation of the following three entries: 'Low-fat milk', 'Cheese with low fat content', and 'Dairy products with low-fat content'. Each of these entries gives valid estimates of intakes. Thus, the single questions regarding dairy foods gave better estimates when used separately.

Moreover, stratifying by gender increased the estimation of intakes for additional food groups. Gender differences in dietary assessment methods have been reported in other studies as well (8, 14, 41). Lee and co-workers (41) emphasise the importance of including different portion sizes for men and women in FFQs, due to their findings that when gender is not considered, greater inaccuracy in dietary intake assessment is found in women compared to in men. In the present study, portions sizes were equal for men and women and they reported intakes of nuts, fish, water, meat, and sugar- and fat-rich foods differently on the NORDIET-FFQ.

Short FFQs have been shown to be able to classify individuals according to intakes of food groups and nutrients (12, 15, 20, 23, 36, 37). In the present study, the NORDIET-FFQ showed fair to satisfactory agreement with respect to ranking individuals by their dietary intake compared to WR. The Spearman's rho ranged from 0.12 to 0.74, with most correlations categorised as fair or satisfactory and statistically significant ($p < 0.01$) (Tables 5 and Supplementary file 2). This is consistent with other similar studies showing a correlation coefficient for foods and nutrients ranging from 0.3 to 0.7 (13, 15, 17, 42). Carlsen and co-workers found that correlations between intakes of fruit and vegetable from a long FFQ and WR ranged from 0.31 to 0.58 (43). Importantly, in the present study, a fair or satisfactory correlation was documented for the foods that are shown to be associated with risk of CRC, such as fruits and vegetables, whole grains, dairy products, red and processed meat, and alcoholic beverages (2–4, 44). However, three food groups showed poor correlations for both genders and in total, that is vegetables, unprocessed meat, and processed meat. Classifying individuals according to intake of food groups may be advantageous in clinical intervention studies as a measure of intervention effects, as well as in a clinical setting to identify patients 'at risk' (23). Based on the high number of fair and satisfactory correlations observed in this study the NORDIET-FFQ's ability to rank participants according to food intake is fair and comparable to other short FFQs (11, 17, 20, 26, 45–48).

Correlation coefficients measures associations between a questionnaire and its reference method but are unable to detect systematic errors that may be of clinical importance (37).

When assessing the agreements between two methods, Bland–Altman plots are recommended (34, 36, 37). Overall, the Bland–Altman plots in the present study showed wide limits of agreement for most of the food groups and a trend towards increased over- or under-reporting with higher mean intakes. However, the mean differences were smaller than 20% between the methods for most of the food groups and the limits of agreement were almost within a daily portion for fruits, vegetables, nuts, fish, meat, and dairy products. Systematic and random errors

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can more easily be revealed by Bland–Altman plots, as the data points are less compressed compared to a scatter plot. For instance, in the present study 'Whole grain products' showed a satisfactory correlation, but a systematic error was revealed by the Bland–Altman plot, showing increasing over-reporting with increasing intakes. Moreover, 'Fish' showed a fair correlation and the distribution of differences against the mean value of the two methods did not show any clear trend. Intakes in the category of 'Vegetables' showed poor correlation and an increased under-reporting with higher intakes, indicating poor ability of the NORDIET-FFQ to measure intakes of vegetables. This may be due to the difficulty of reporting portions of vegetables, since these foods are often included in dishes, compared to fruits, which are more often eaten raw in one unit (43). However, the questionnaire was good in measuring intakes of vegetables on the group level and according to the recommendations. Thus the NORDIET-FFQ gave a fairly good estimate of intake for several of the food groups on the group level compared to the WR standard.

The NORDIET-FFQ was able to detect individuals not fulfilling the Norwegian FBDG (i.e. sensitivity) for 10 out of 20 recommendations, covering most of the food groups shown to be associated with CRC risk (i.e. fruits and vegetables, whole grains, processed meat, alcohol intake, dairy products) (1–4, 44). Moreover, the NORDIET-FFQ was able to identify individuals who fulfilled 13 out of 20 recommendations (i.e. specificity) (Table 6).

Strengths and limitations

Attenuation of agreement between two methods can occur due to different time period covered by the methods. In the present study we compared a retrospective method (NORDIET-FFQ) with a prospective method (WR). A limitation of the study may be that the NORDIET-FFQ asked for dietary intake over the previous 1–2 months, whereas the WR recorded dietary intakes for the subsequent week. However, the short time period covered by this study design, approximately 2.5 months, would probably limit the error between NORDIET-FFQ and WR recording (8, 14). Timing and sequence for the test and reference method is important in validation studies, of which the test method should be administrated prior to the reference method (14). In the present study, the participants completed the FFQ prior to the WR and thereby avoided any learning effects from the reference method. Seasonal effects of dietary intakes were not expected since dietary intakes were collected from all seasons during a year. Moreover, variation in reporting of dietary intakes may be attributed to the comparison between closed and open ended methods (14). Study participants were recruited from both arms of the intervention. The purpose of an evaluation study is to compare estimates of intake of test and reference method. Hence, the diet of the participants should be assessed alike and should not be dependent on differences in diet among the participants. Both groups were equally exposed to the dietary assessment methods, anthropometric measurements, and biological samplings, as well as the direct contact with the researchers. However, we cannot rule out that the intervention group might have been more conscious about the registration of food and beverages than the participants in the non-intervention group.

FFQs are associated with limitations such as fixed food list, memory, and perception of portion sizes (8). However, WRs control these errors due to their independency of memory and direct measurement of food intakes (8, 16). In order to be used as a standard reference method in assessing the validity of questionnaires, WRs should cover a sufficient number of days to represent average dietary intakes (8). In the present study this was taken into account, since all the WRs recorded dietary intakes over 7 consecutive days.

As the aim of the NORDIET-FFQ was to measure adherence to the dietary guidelines, an aggregation of the single foods was needed. Hence, using the aggregated questions conforming to the Norwegian FBDG in the NORDIET-FFQ resulted in less detailed information of food intake. However, short FFQs containing aggregated questions have been shown to capture nearly as much information on dietary intakes as long FFQs (8, 16).

Conclusion

The NORDIET-FFQ was able, on a group level, to estimate intakes of most food groups related to the Norwegian FBDG, such as fruits, vegetables, nuts, fish, dairy products, meat, beverages, and sugar- and fat-rich foods. Moreover, the NORDIET-FFQ was able to rank individual intakes and to identify those individuals in need of dietary counselling for foods that are shown to be associated with risk of CRC, such as fruit and vegetables, whole grains, red meat, alcoholic beverages, and dairy products. The NORDIET-FFQ was not able to rank individual intakes of processed meat, unprocessed meat, and vegetables. Overall, the NORDIET-FFQ gives valid estimates of dietary intake according to the Norwegian FBDG.

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Conflict of interest and funding

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Authors' contributions

HBH had primary responsibility for writing the manuscript. HBH, MHC, IP, SKB, AJS, ASK, LFA, CH, SS, SB, and RB contributed to the conception and design of the study, analysis and interpretation of the data, and drafting of the manuscript. HBH, AJS, IP, and ASK contributed to acquisition of data. All authors contributed to the writing and approval of the final manuscript.

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Supplementary file 1. Food and beverages from NORDIET FFQ and WR, all participants in total and stratified by gender

Food and beverages[a]	NORDIET-FFQ (n=81)			WR (n = 81)			p-values[c]		
	Total	Men	Women	Total	Men	Women	p_{tot}	p_{men}	P_{women}
	Median (P_5, P_{95})[b]	Median (P_5, P_{95})[b]	Median (P_5, P_{95})[b]	Median (P_5, P_{95})[b]	Median (P_5, P_{95})[b]	Median (P_5, P_{95})[b]			
Fruit and berries, g/d									
Fruit[d]	100 (21, 298)	106 (17,321)	93 (19, 326)	114 (0,370)	108 (0,466)	123 (0,353)	0.43	0.38	0.76
Berries	8 (0,147)	8 (150)	12 (0,154)	0 (0,98)	0 (0,81)	21 (0,129)	0.88	0.19	0.3
Dried fruit	4 (0,106)	0 (0,32)	0 (0,168)	0 (0,20.5)	0 (0,14)	0 (0,32)	<0.001	<0.001	0.002
Vegetables, g/d									
Garlic	0 (0,3)	0 (0,2)	0 (0,4)	0 (0,3)	0 (0,1.4)	0 (0,4)	0.001	0.014	0.003
Onion	6 (0,23)	5 (0,23)	6 (0,18)	7 (0,36)	9 (0,59)	6 (0,27)	0.02	0.019	0.44
Tomato	30 (0,181)	28 (0,114)	44 (0,290)	21 (0,74)	17 (0,98)	23 (0,75)	<0.001	0.017	0.002
Tomato sauce	4 (0,29)	7 (0,29)	4 (0,29)	6 (0,84)	8 (0,86)	5 (0,87)	0.01	0.15	0.04
Mixed salad	22 (0,71)	18 (0,71)	22 (0,93)	26 (0,106)	25 (0,105)	28 (0,157)	0.103	0.25	0.23
Other vegetables	52 (8,157)	52 (0,158)	43 (0,234)	73 (0,179)	70 (20,192)	83 (9,179)	0.015	0.015	0.34
Nuts, g/d									
Nuts (salted + unsalted)	9 (0,39)	11 (0,37)	7 (0,39)	2.4 (0, 32)	2 (0,46)	3 (0,33)	0.002	0.013	0.09
Salted nuts	2 (0,22)	4 (0,28)	0 (0,23)	0 (0,22)	0 (0,27)	0 (0,21)	0.006	0.03	0.58
Cereals (g/d)									
Sweetened cereals	0 (0,14)	0 (0,29)	0 (0,0)	5 (0,59)	0 (0,31)	0 (0,25)	0.37	0.74	0.07
Unsweetened cereals	7 (0,67)	0 (0,68)	15 (0,71)	0 (0,26)	0 (0,58)	12 (0,64)	0.37	0.75	0.43
Beverages (g/d)									
Beverages with no added sugar	28 (0,396)	57 (0,882)	28 (0,375)	0 (0, 507)	12 (0,620)	0 (0,269)	0.08	0.16	0.35
Juice	56 (0,274)	28 (0,252)	58 (0,284)	66 (0,370)	54 (0,333)	90 (0,526)	0.45	0.8	0.39
Low fat milk	114 (0,372)	114 (0,504)	93 (0,312)	108 (0,560)	138 (0,621)	100 (0,369)	0.28	0.17	0.9
Whole milk	0 (0,182)	0 (0,186)	0 (0,165)	0 (0,116)	0 (0,101)	0 (0,132)	0.12	0.07	0.8
Filtered coffee	178 (0, 1160)	125 (0,814)	233 (0,1678)	329 (0805)	352 (3,814)	296 (0,764)	0.003	0.001	0.49
Other coffee (espresso, etc)	0 (0, 663)	0 (0,1199)	0 (0,385)	0 (0, 150)	0 (0,64)	0 (0,289)	<0.001	<0.001	0.049

Tea	213 (0,814)	65 (0,1284)	279 (0,558)	71 (0,589)	43 (0,631)	109 (0,507)	<0.001	0.023	<0.001
Beer with alcohol, g/d	0 (0,508)	140 (0,897)	0 (0,160)	0 (0, 429)	36 (0,963)	0 (0,243)	0.02	0.04	0.46
Liquor, g/d	0 (0,12)	0 (0,12)	0 (0,29)	0 (0,25)	0 (0,27)	0 (0,29)	0.08	0.23	0.15
Wine with alcohol, g/d	31 (0,136)	31 (220)	30 (0,125)	43 (0, 281)	34 (0,387)	46 (0,181)	<0.001	0.006	0.008
Cakes, dessert, candy (g/d)									
Cakes	17 (0,101)	8 (0,64)	17 (0,117)	26 (0,105)	22 (0,133)	32 (0,72)	0.02	0.006	0.12
Dessert	0 (0,81)	0 (0,90)	13 (0,84)	4 (0,65)	0 (0,74)	9 (0,68)	0.95	0.79	0.88
Candy	7 (0,43)	11 (0,43)	7 (0,45)	3 (0,31)	2 (0,39)	7 (0,31)	0.006	<0.001	0.83
Chips	0 (0,21)	0 (0,30)	0 (0,18)	0 (0,14)	0 (0,14)	0 (0,23)	0.18	0.09	0.75
Bread (g/d)									
Bread (60 % cereals) with 0-25 % wholemeal flour	0 (0,57)	0 (0,83)	0 (0,33)	11 (0,60)	16 (0,83)	9 (0,61)	<0.001	0.001	0.001
Bread (60 % cereals) with 25-50% wholemeal flour	0 (0,144)	0 (0,207)	0 (0,144)	3 (0,114)	8 (0,122)	0 (0,75)	0.84	0.58	0.55
Bread (60 % cereals) with 50-75 wholemeal flour	69 (0,360)	90 (0,360)	60 (0,246)	34 (0,143)	37 (0,195)	33 (0,110)	<0.001	0.001	0.005
Bread (60 % cereals) with 75-100% wholemeal flour	0 (0,180)	0 (0,240)	0 (0,180)	11 (0,100)	9 (0,121)	13 (0,106)	0.34	0.38	0.71
White crispbread (0-25% wholegrain)	0 (0,12)	0 (0,12)	0 (0,24)	0 (0,0)	0 (0,0)	0 (0,0)	0.02	0.06	0.14
Wholemeal crispbread (100% wholegrain)	14 (0,84)	14 (0.0,67)	14 (0,59)	3 (0,51)	3 (0.0,50)	7 (0,59)	<0.001	<0.001	0.002
Spreads on bread (g/d)[e]									
Cheese with high fat content	45 (0,155)	6 (0,29)	6 (0,24)	21 (0, 64)	20 (0,73)	21 (2,54)	<0.001	<0.001	<0.001
Cheese with low fat content	0 (0,155)	0 (0,29)	1 (0,22)	0 (0,31)	0 (0,32)	3 (0,35)	0.97	0.09	0.054

Sweetened spreads	3 (0,43)	3 (0,70)	3 (0,21)	7 (0,52)	6 (0,37)	9 (0,88)	0.007	0.95	0.001
Dairy products (i.e. sour cream, yoghurt etc.)									
Dairy products with high fat content	0 (0,113)	0 (0,131)	4 (0,145)	1 (0,36)	3 (0,53)	0 (0,28)	0.55	0.43	0.06
Dairy products with low fat content	7 (0,71)	7 (0,65)	11 (0,84)	18 (0,168)	1 (0,156)	35 (0,211)	0.006	0.33	0.006
Fish for dinner (g/d)[f]									
Processed fish	13 (0, 52)	13 (0,52)	13 (0,52)	0 (0,70)	0 (0,79)	15 (0,60)	0.68	0.78	0.80
Lean fish, g/d	20 (0,60)	20 (0,73)	20 (0,62)	14 (0,64)	21 (0,72)	13 (0,72)	0.32	0.96	0.08
Meat for dinner (g/d)									
Non-processed red meat	21 (0,65)	22 (0,81)	21 (0,48)	24 (0,109)	21 (0,96)	29 (0,129)	0.07	0.33	0.08
Processed red meat	21 (0,65)	21 (0,86)	21 (0,67)	40 (0,107)	60 (5,134)	23 (0,59)	<0.001	<0.001	0.057
Non-processed white meat	21(0,87)	21 (0,89)	21 (0,67)	14 (0,70)	13 (0,70)	14 (0,75)	0.05	0.19	0.11
Processed white meat	0 (0, 44)	21 (0,87)	0 (0,48)	0 (0,30)	0 (0,27)	0 (0,33)	0.002	0.005	0.17
Rice and pasta (g/d)									
White rice	0 (0,34)	0 (0,43)	0 (0,36)	0 (0,44)	0 (0,76)	0 (0,43)	0.002	0.67	0.02
Wholegrain rice	0 (0,33)	0 (0,43)	0 (0,24)	0 (0.24)	0 (0,34)	0 (0,25)	0.47	0.16	0.01
White pasta	0 (0,73)	0 (0,73)	0 (0,73)	0 (0,34)	0 (0,39)	0 (0, 20)	0.003	0.009	0.18
Wholegrain pasta	0 (0,73)	0 (0,73)	0 (0,76)	0 (0,24)	0 (0,19)	0 (0,25)	<0.001	0.01	0.01
Dietary supplements									
Cod liver oil (ml/d)	0 (0,10)	0 (0,9)	0 (0,10)	0 (0,47)	0 (0,45)	0 (0,55)	0.01	0.2	0.03
Cod liver oil/fish oils in capsules	0 (0,2)	0 (0,3)	0 (0,2)	0 (0,2)	0 (0,2)	0 (0,3)	0.003	0.18	0.02
Vitamin D (capsule/d)	0 (0, 1)	0 (0,1)	0 (0,1)	0 (0,0)	0 (0,0)	0 (0,1)	<0.001	0.007	0.01
Multivitamin (tablets/d)	0 (0, 1)	0 (0,1)	0 (0,1)	0 (0,1)	0 (0,0)	0 (0,2)	0.007	0.01	0.16

[a]Food groups based on Supplementary file 1

[b] P_5= 5 percentile, P_{95}= 95 percentile

[c] Wilcoxon signed rank test, p-values for median intake of food groups from NORDIET-FFQ and WR, both total and between genders

[d] Fruit includes the following sub-questions: large fruit, medium fruit, small fruit in NORDIET-FFQ

[e] Spreads like “fish”, “red meat”, “white meat” and “fruit and vegetables” are not included in this table, but are included in fatty fish , meat products and fresh fruits and vegetables, respectively

[f] Fatty and lean fish for dinner/lunch can be found in Table 3.

NORDIET-FFQ, NORDIET Food Frequency Questionnaire; WR, 7-day weighed food records

Supplementary file 2. Spearman Rank Order Correlation (r) of food and beverages between NORDIET-FFQ and WR, all participants in total and stratified by gender

Single food questions in NORDIET-FFQ[a]	**Total**	**Men**	**Women**
Fruit and berries, g/d	**r**	**r**	**r**
Fruit[b]	0.43*	0.48*	0.43*
Berries	0.46*	0.40*	0.53*
Dried fruit	0.51*	0.41*	0.54*
Vegetables, g/d			
Garlic	**0.36***	0.26	**0.45***
Onion	**0.42***	**0.44***	**0.36**
Tomato	**0.43***	**0.45***	**0.34**
Tomato sauce	0.15	**0.35***	-0.05
Mixed salad	0.26	0.21	**0.30**
Other vegetables	0.20	0.07	**0.33**
Nuts, g/d			
Nuts (salted + unsalted)	0.40*	0.31*	0.49*
Salted nuts	0.25	0.12	0.48*
Cereals (g/d)			
Sweetened cereals (25-50% wholegrain)	0.26	0.38	-----
Unsweetened cereals (75-100% wholegrain)	0.55*	0.46*	0.58*
Beverages (g/d)			
Beverages, no added sugar	0.40	0.39*	0.37*
Juice	0.65*	0.66*	0.62*
Low fat milk	0.78*	0.82*	0.75*
Whole milk	0.57*	0.58*	0.58*
Filtered coffee	0.56*	0.41*	0.76*
Other coffee (espresso, etc)	0.40	0.46*	0.39
Tea	0.82*	0.91*	0.74*
Beer with alcohol, g/d	0.57*	0.69*	0.26
Wine with alcohol, g/d	0.52*	0.55*	0.52*
Liquor, g/d	0.81*	0.82*	0.78*
Cakes, dessert, candy (g/d)			
Cakes	0.34*	0.33	0.35
Dessert	0.46*	0.37	0.55*
Candy	0.42*	0.31	0.63*
Chips	0.60*	0.56*	0.65*
Bread (g/d)			
Bread (60 % cereals) with 0-25 % wholemeal flour	0.19	0.22	0.13
Bread (60 % cereals) with 25-50% wholemeal flour	0.21	0.22	0.04
Bread (60 % cereals) with 50-75 wholemeal flour	0.51*	0.57*	0.45*
Bread (60 % cereals) with 75-100%	-0.01	-0.006	0.04

wholemeal flour			
White crispbread (0-25% wholegrain)	-0.034	------	-0.049
Wholemeal crispbread (100% wholegrain)	0.46*	0.66*	0.17
Spreads on bread (g/d)[c]			
Cheese with high fat content	0.37*	0.32	0.51*
Cheese with low fat content	0.57*	0.51*	0.59*
Sweetened spreads	0.64*	0.65*	0.71*
Dairy products			
Dairy products with high fat content	0.25	0.18	0.39
Dairy products with low fat content	0.29*	0.36	0.16
Fish for dinner (g/d)[d]			
Lean fish	0.33*	0.40*	0.34
Processed fish	0.39*	0.38	0.44*
Meat for dinner (g/d)			
Unprocessed red meat	0.31*	0.25	0.40
Processed red meat	0.22	0.19	0.11
Unprocessed white meat	0.25	0.18	0.36*
Processed white meat	0.10	-0.08	0.38
Rice and pasta (g/d)			
White rice	0.37*	0.35	0.51*
Whole grain rice	0.20	-0.2	0.60*
White pasta	0.08	0.33	-0.02
Whole grain pasta	0.34*	0.45*	0.2
Dietary supplements			
Cod liver oil (ml/d)	0.74*	0.65*	0.78*
Cod liver oil/fish oils in capsules	0.29*	0.45*	0.14
Vitamin D (capsule/d)	0.42*	---	0.58*
Multivitamin (tablets/d)	0.47*	0.36	0.16

*Correlation is significant at the 0.05 level (2-tailed)

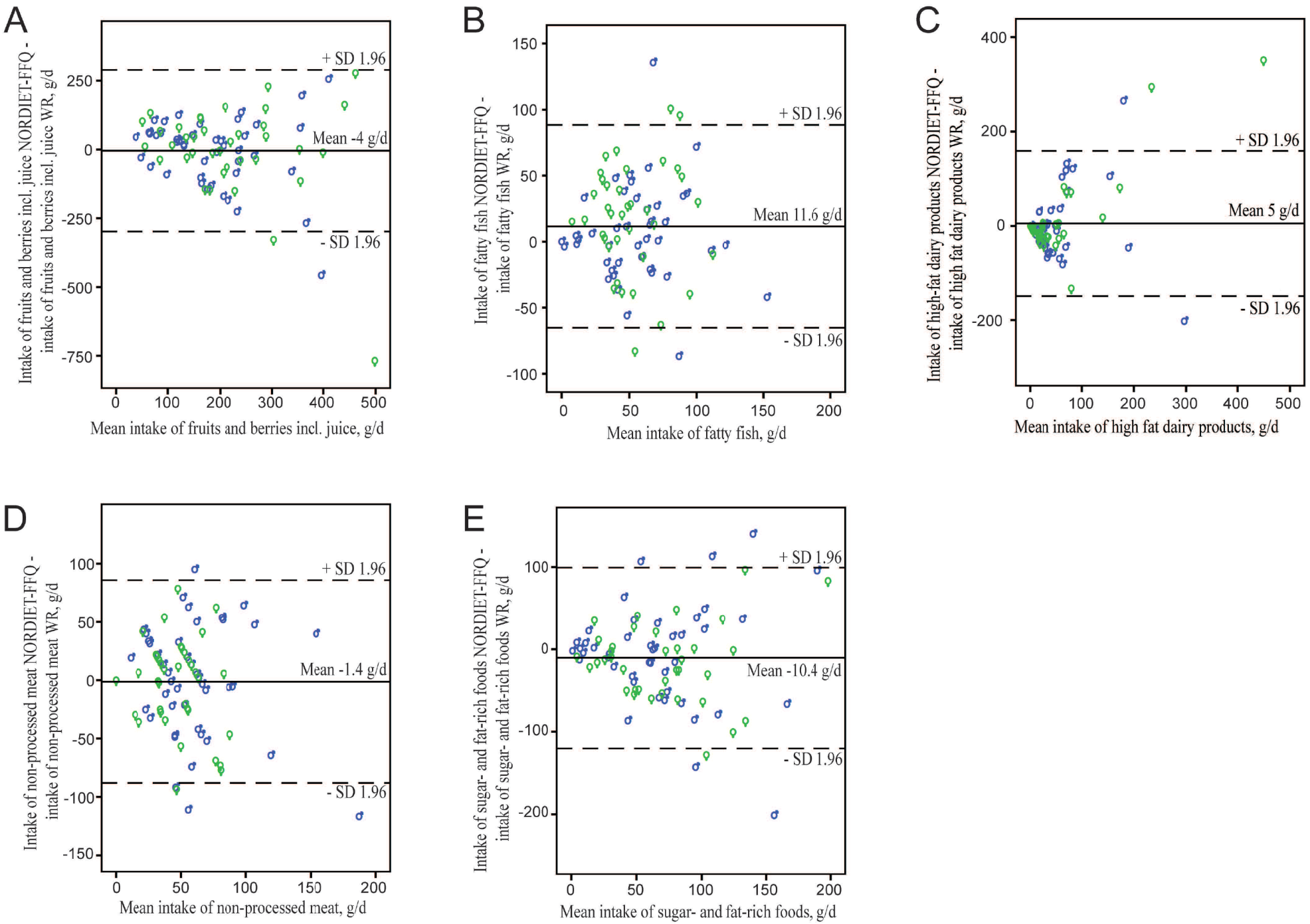
[a]Food groups based on Supplementary file 1

[b] Fruit includes the following sub-questions: large fruit, medium fruit, small fruit in NORDIET-FFQ

[c]Spreads like "fish", "red meat", "white meat" and "fruit and vegetables" are not included in this table, but are included in fatty fish, meat products and fresh fruits and vegetables, respectively

[d]Fatty and lean fish for dinner/lunch can be found in Table 3

NORDIET-FFQ, Short Food Frequency Questionnaire; WR, 7-day weighed food record


A
Intake of fruits and berries incl. juice NORDIET-FFQ - intake of fruits and berries incl. juice WR, g/d
+ SD 1.96
Mean -4 g/d
- SD 1.96
Mean intake of fruits and berries incl. juice, g/d
B
Intake of fatty fish NORDIET-FFQ - intake of fatty fish WR, g/d
+ SD 1.96
Mean 11.6 g/d
- SD 1.96
Mean intake of fatty fish, g/d
C
Intake of high-fat dairy products NORDIET-FFQ - intake of high fat dairy products WR, g/d
+ SD 1.96
Mean 5 g/d
- SD 1.96
Mean intake of high fat dairy products, g/d
D
Intake of non-processed meat NORDIET-FFQ - intake of non-processed meat WR, g/d
+ SD 1.96
Mean -1.4 g/d
- SD 1.96
Mean intake of non-processed meat, g/d
E
Intake of sugar- and fat-rich foods NORDIET-FFQ - intake of sugar- and fat-rich foods WR, g/d
+ SD 1.96
Mean -10.4 g/d
- SD 1.96
Mean intake of sugar- and fat-rich foods, g/d

III

Validation of two short questionnaires assessing physical activity in colorectal cancer patients

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Validation of two short questionnaires assessing physical activity in colorectal cancer patients

Abstract

Background: In order to investigate the impact of adherence to recommendations of physical activity and sedentary time on health outcomes in clinical trials, there is a need for feasible tools such as questionnaires that can give representative estimates of these measures. The primary aim of the present study was to validate two such questionnaires and their ability to estimate adherence to the recommendations of physical activity defined as moderate-to-vigorous physical activity or moderate physical activity of at least 150 min/week in colorectal cancer patients. Secondarily, self-reported sedentary time from the HUNT-PAQ was also evaluated.

Methods: Participants from ʻThe Norwegian dietary guidelines and colorectal cancer survival-study' (CRC-NORDIET study) completed two short questionnaires; the NORDIET-FFQ (n=78) and the HUNT-PAQ (n=77). The physical activity monitor SenseWear Armband Mini was used as the reference method during seven consecutive days.

Results: The NORDIET-FFQ provided better estimates of time in moderate-to- vigorous physical activity and moderate physical activity than the HUNT-PAQ. The NORDIET-FFQ was unable to rank individual time in moderate-to- vigorous physical activity and moderate physical activity (Spearman`s rho=0.08, p=0.509 and Spearman`s rho rho= 0.01, p= 0.402, respectively). All intensities were under-reported by the HUNT-PAQ, but ranking of individual time in moderate physical activity and sedentary time were acceptable among women only (Spearman`s rho=0.37, p=0.027 and Spearman`s rho=0.36, p=0.035, respectively). The HUNT-PAQ correctly classified 71% of those not meeting the recommendations (sensitivity), and the NORDIET-FFQ correctly classified 63% of those

who met the recommendations (specificity). About 67% and 33% reported to meet the recommendation of moderate-to- vigorous physical activity with the NORDIET-FFQ and HUNT-PAQ, respectively, whereas 55% actually met the moderate-to- vigorous physical activity according to the SenseWear Armband Mini.

Conclusions: The validity of the two short physical activity questionnaires was investigated in colorectal cancer patients. Both questionnaires may be useful in assessing adherence to physical activity recommendations. However, it is important to be aware of the limitations documented in the present study.

Trial registration: The study is registered on the National Institutes of Health Clinical Trials (www.ClinicalTrials.gov; Identifier: NCT01570010).

Keywords: short questionnaire, physical activity, sedentary time, SenseWear Armband Mini, physical activity recommendations

Background

The preventive effect of physical activity (PA) on risk of colorectal cancer is well-established [1-3]. However, an increasing number of studies also examine beneficial effects of PA during cancer treatment as well as in the posttreatment period [4-16], such as decreased all-cause mortality, increased disease-free survival, improved physical function and quality of life [5, 6, 11-13, 17, 18]. Moreover, reduced sedentary time, such as sitting during daytime, may be associated with reduced mortality and lower risk of recurrence in cancer patients [19-22].

The recommendations of PA for cancer patients and survivors provided by the American Cancer Society [23] emphasize that exercise is safe and feasible during cancer treatment, and improves outcomes such as physical function, fatigue and completion of chemotherapy [23]. The American Cancer Society, the World Health Organization and others [24-27] recommend at least 150 minutes of moderate intensity PA (MPA) or 75 minutes of vigorous intensity PA (VPA) per week or an equivalent combination. In 2011, the Norwegian Directorate of Health published the Norwegian Food-Based Dietary Guidelines (FBDG) which also includes similar recommendations on PA as well as for sedentary time [3].

In Norway, colorectal cancer (CRC) is the third most common cancer type, and the incidence is among the highest in Europe [28]. Implementing the recommendations of PA and incorporating specific exercises in the clinical care may improve the health outcomes of CRC patients [1-3, 24].

In order to estimate adherence to PA recommendations according to the Norwegian FBDG in a Norwegian CRC population, a valid and accurate physical assessment tool is needed. Importantly, assessment of adherence to the PA recommendations is required in counselling

and when evaluating effectiveness of intervention studies. The use of objective monitors to record PA has increased during recent decades and gives valid and reliable data on intensity of PA and energy expenditure [29]. However, these activity monitors are expensive and time consuming for the clinician and researcher, particularly when recording PA in larger populations. Therefore, less expensive and easier methods are required to measure adherence to PA recommendations.

The most common self-reporting method to assess PA is the use of questionnaires [30, 31]. Over the past 2 or 3 decades, more than 30 PA questionnaires have been developed and validated [32]. Long questionnaires are challenging to complete for cancer patients often experiencing treatment and disease related side-effects such as fatigue and functional decline [33-36]. Questionnaires which contains few and well-defined questions regarding the different intensities of PA may be more suitable for this group of patients [37].

Although many previous questionnaires have been successfully used to assess PA, there is no questionnaire specifically designed to assess adherence to the PA recommendations as defined in Norwegian FBDG. For a clinical trial in colorectal cancer patients [38], a new short semi-quantitative questionnaire (NORDIET-FFQ) was developed to measure adherence to the Norwegian FBDG. The NORDIET-FFQ includes two questions on PA related to intensity levels similar to MPA and VPA. Another short questionnaire, the HUNT-PAQ [39] has been used in large healthy populations in Norway; however, this questionnaire has not previously been validated in a CRC population.

Thus, the primary aim of the present study was to validate the two short questionnaires and their ability to estimate adherence to the PA recommendations according to the Norwegian FBDG. Secondarily, self-reported sedentary time from the HUNT-PAQ was also evaluated.

Methods

Subjects and study design

The present validation study was a sub-study of the ongoing CRC-NORDIET study, of which design and methods have been published elsewhere [38]. In brief, the aim of the CRC-NORDIET study is to investigate the effect of a diet similar to the Norwegian FBDG [3] on disease-free and overall survival among CRC patients post-diagnosis [38]. The risk factors shown to be related to CRC, i.e. diet and physical activity, are included in the Norwegian FBDG [40]. The CRC-NORDIET study is a prospective randomised controlled intervention trial, randomising 500 CRC patients into one of two study groups (i.e. 250 to diet intervention group and 250 to the control group). All patients are invited to the Study centre 3 times during the intensive 1-year intervention (i.e. at baseline 2-9 months post-surgery and at the two visits 6- and 12 months after baseline), and subsequently followed up for 14 years. Both study groups are offered equal recommendations on PA [38].

All patients from both study groups in the CRC-NORDIET study, who attended the follow-up at 6 months after baseline of intervention (i.e. 2-9 months post-surgery) from January 2014 to October 2015, were invited to take part in the present validation study. The patients were men and women aged 50-80 years old, with a confirmed CRC (ICD-10 C18-20), and staged I-III (i.e. locoregional disease without metastasis) according to the TNM staging system [41]. None of the patients included in the validation study underwent chemotherapy during the time-frame covered by the physical assessment methods used in the validation

study (e.g. mean time from last chemotherapy injection to the start of the validation study (i.e 6 months after baseline) was 155 days among the 15% who received adjuvant treatment). During the 6-months visit, the patients completed the self-administered NORDIET-FFQ and HUNT-PAQ. In addition, they received the SenseWear Armband Mini (SWA), which was returned by mail to the CRC-NORDIET-study at the end of the test period of seven days. Exclusion criteria for the present study were pacemaker implantation, not completed questionnaires or not wearing the SWA.

Characteristics of the participants

To characterize the subjects, anthropometric measurements (weight, height, and hip-and waist circumference) and physical tests (hand-grip strength, 30-second sit-to-stand test and 6-minutes walking test) were measured by the researchers of the CRC-NORDIET study during all visits at the Study centre, as previously described elsewhere [38]. In addition, education level and smoking status were self-reported by completion of questionnaires during the visits at the Study centre. Information about tumour location status was retrieved from medical records in cooperation with the hospital personnel. Energy expenditure (kJ/d) was estimated from the SWA.

Short semi-quantitative frequency questionnaire (NORDIET-FFQ)

The NORDIET-FFQ (available upon request to corresponding author), was designed to report PA in recent weeks (i.e.the last 1-2 months). The participants completed the NORDIET-FFQ at the study centre and the questionnaires were checked for completeness by the researchers, so that incomplete answers could be corrected. The NORDIET-FFQ was scanned and the image files translated into data files using the Cardiff Teleform 2006 Software (6.0) (Datascan). The last two questions in the NORDIET-FFQ asked for PA with two different

intensities, MPA and VPA estimated in pre-defined intervals of frequency per week and duration in minutes. The explanatory texts for both PA questions included examples of typical activities: moderate intensity was exemplified by brisk walking, household chores or other activities resulting in slight breathlessness, and vigorous intensity was exemplified by running, cross-country skiing or other activities resulting in high breathlessness. The question about frequency contained different responses in times per week (time divided by seven) coded as follows: *0=0, 1=0.14, 2=0.29, 3=0.43, 4=0.57, 5=0.71, 6-7 =0.93* and *8+ =1.37 (*added 20% to 8 and divided by 7). Moreover the responses of duration in minutes were coded as follows: *1-4=2, 5-9=7, 10-15=12.5, 16-20=18, 21-30=25.5, 31-45=38, 46-60=53* and *60+=72* (added 20% to 60). Amounts in minutes of PA per day for each intensity were calculated by multiplying frequency (i.e. times per day) with duration (i.e. minutes each time). This resulted in variables of total-MPA and total-VPA, of which all minutes within each intensity were included (Additional file 1 and 2). Additionally, categories of 10-minute bouts were computed and defined as ten or more consecutive minutes within each intensity level. This resulted in data on 10-minute bouts of MPA and VPA.

HUNT (The Nord-Trøndelag Health Study) Physical activity questionnaire (HUNT-PAQ)

The HUNT-PAQ was based on the questionnaire used in the HUNT 3-study [39]. Only the five questions about PA as described in Kurtze et al. [42] were used. The question about frequency contained the following responses: *Never* and *Less than once a week,* both coded as 0, *Once a week* coded as 1, *2-3 times a week* coded as 2.5, and *Almost every day* coded as 7. The question about duration of activity contained the following responses: *Less than 15 minutes* coded as 12 (subtracted 20% from 15), *15-29* minutes coded as 22, *30-1 hour* coded as 45 and *more than 1 hour* coded as 72 (added 20% to 60). The products of frequency and

duration were weighted by intensity level, i.e. *Low*, *Moderate* or *Vigorous* coded as 1, 2 and 3, respectively. The low intensity level was not evaluated in the present study. Additionally, there was a question about daily sedentary time in hours on a usual day (not included sleeping at night-time). The questionnaire generated data on activities in bouts of 10 and more consecutive minutes for each intensity level, such as MPA and VPA.

Objective physical activity measurement

The objective PA monitor SenseWear Armband Mini (SWA) (BodyMedia, Pittsburgh, Pennsylvania, USA) was used to record daily PA and energy expenditure during seven consecutive days [43]. A priori, we defined a valid day of recording if the wear time was ≥ 80% of a 24-h sampling period. The SWA has previously been validated against double-labelled water [44], indirect calorimetry [45] and other accelerometers [46] in adults and cancer patients. It monitors physiological data such as heat flux, galvanic skin response, 3-axis accelerometer and skin temperature. The SWA was pre-programmed by the researcher with the co-predictors such as weight, height, birth date, sex, smoking status (smoker/non-smoker) and whether the participant was left or right handed, and placed around the triceps muscle halfway on the upper non-dominant arm. The participants were instructed to continue their normal activity level while wearing the SWA. Water-based activities were not recorded by the SWA because the monitor is not waterproof. Participants were asked to remove the SWA when performing activities in water. All data were retrieved from the SWA to a computer with the SenseWear Professional Software Version 7.0 BodyMedia Inc (Pittsburgh, Pennsylvania, USA).

Activity intensities were integrated into algorithms, providing estimates of energy expenditure expressed in metabolic equivalents (METs). The definition of 1 MET is the

amount of oxygen consumed while sitting at rest and is equal to 3.5 ml O_2 per kg bodyweight per min [47]. Moderate and vigorous intensities were defined as 3-6 and >6 METs, respectively, as calculated by Ainsworth and coworkers [48, 49]. Sedentary time was defined as all daily activities ≤1.5 METs, of which nighttime sleep was removed (a priori defined as from 12 midnight to 6.00 a.m.). All activities were calculated and expressed in minutes or hours per week (sedentary time).

The SWA records all intensities in 1-minute intervals, which were translated into different categories of data such as total-MPA and total-VPA. Furthermore, the data were also computed into 10-minutes intervals, which were defined as ten or more consecutive minutes within the relevant intensity level. The bouts of 10-minutes were calculated for the two intensity levels, which gave data on bouts of 10-minutes for MPA and VPA.

Recommendations of physical activity

The CRC patients were advice to follow the recommendations of moderate-to-vigorous intensity PA (MVPA), MPA and VPA. MVPA was defined as 'MPA + (VPA*2)' [50] and the cut-off points for fulfilling recommendations of MVPA and MPA were at least 150 minutes per week, and at least 75 minutes per week for VPA. The activities should be in bouts of 10 and more consecutive minutes.

Statistical analysis

Data were analysed using IBM SPSS Statistics, version 22. All p-values were two-sided and with a significance level of 5%. All data were checked for normal distribution by evaluating histograms, normal Q-Q-Plots and Kolmogorov-Smirnov test ($p>0.05$).

All anthropometric measurements and other characteristics of the study population were normally distributed and are presented as means with standard deviations (SD). The categorical data are presented as frequency and percentage. Most of the estimates of PA from the SWA, NORDIET-FFQ and HUNT-PAQ were not normally distributed and are presented as medians and 5^{th} - and 95^{th} percentile. Categorical variables were compared by the Fischer exact test and Pearson chi-square test. Wilcoxon Signed-Rank test for paired data was used to check for difference in median activity between the two questionnaires compared to the SWA. Bland-Altman plots with limits of agreements were used to explore the differences between the measurements from the two methods (i.e. questionnaire minus SWA) plotted against the average of the two measurements, for each individual subject, as well as to identify outliers [51, 52]. Systematic under- or over-reporting was tested by linear regression with MVPA and MPA from SWA as the independent variable and the difference between the questionnaires and SWA as the dependent variable. Spearman Rank Order Correlation (rho) was calculated to explore the strength of the relationship between the continuous variables from the two different methods, and the ranking of individual time in PA. The ability of the NORDIET-FFQ and the HUNT-PAQ to classify the individual`s activity intensity into the same category as the SWA was estimated by the use of sensitivity and specificity analysis. Sensitivity was defined as the number of subjects reported not to fulfil the MVPA with both questionnaires and SWA as a percentage of those who had reported not to fulfil the MVPA with the SWA. Specificity was defined as the number of subjects reported to fulfil the MVPA with both questionnaires and SWA as a percentage of those who had reported to fulfil the MVPA with the SWA.

Sample size

A sample size of 38 men and 38 women were needed to detect a Pearson correlation coefficient of 0.5 or higher between the test-method (i.e. questionnaires) and the reference method (i.e. SWA), with a significance level of 5 % and power of 90 % [53]. With an expected consent rate of 90% and exclusion rate of maximum 5%, we aimed to invite 90 participants in order to include 76 participants to the present study.

Results

Of the 88 invited participants, three were excluded due do pacemaker implantation and 7 declined to participate. Hence, seventy eight participants used the SWA and completed the NORDIET-FFQ, whereas 77 of these also completed the HUNT-PAQ. General characteristics of the participants are presented in Table 1. Mean age of the participants was 64.8 years, and did not differ significantly between men and women (Table 1). Mean time between surgery and baseline was 120.7 days ± 41.4 days (mean ±SD) and between baseline and 6-months visit was 184.4 ± 39.1 days (mean ± SD). Total energy expenditure estimated from the SWA was 11.4 and 9.0 MJ for men and women, respectively. About 8% of the participants were smokers and 51% were highly educated (college/university education) (Table 1).

// Table 1 placed here//

Moderate-to-vigorous intensity physical activity recorded from the NORDIET-FFQ, HUNT- PAQ and SWA

Participants wore the SWA monitors for 97.9 ± 3.8 % (mean, ± SD) of the time during 6.2 ± 0.8 days (mean, ± SD) of monitoring.

Median duration of PA estimated from the NORDIET-FFQ, HUNT-PAQ and the SWA is presented in Table 2. There was no significant difference between the NORDIET-FFQ and SWA for the measure for activity of moderate-to-vigorous intensity PA (MVPA), either for the total population ($p=0.897$) or when analyzing sexes separately. The HUNT-PAQ, however, significantly measured MVPA differently on a group level compared to SWA ($p<0.001$).

// *Table 2 placed here//*

Mean differences in PA measures (i.e. questionnaire minus SWA) with corresponding limits of agreements between questionnaires and the SWA are shown in Bland Altman plots in Figure 1. MVPA (Figure 1A) was reported only 4% differently with the NORDIET-FFQ compared to the SWA (mean difference and limits of agreement -12 ± 624 minutes/week). The under-estimation of MVPA (Figure 1 D) with the HUNT-PAQ was 58% compared to SWA (mean difference and limits of agreement -162 ±576 minutes/week). Moreover, the Bland Altman-plot for MVPA revealed an increase in the differences between both questionnaires and SWA with increased PA level. Additionally, the differences were randomly and evenly distributed above and below the mean difference for both questionnaires compared to SWA up to about 250 min/week (Figure 1 A and D). The slope of the linear regression was negative and significant for both questionnaires ($\beta= -0.79$, $p<0.001$(NORDIET-FFQ) and $\beta= -0.85$, $p<0.001$ (HUNT-PAQ)), indicating under-reporting at higher levels of PA (MVPA from SWA as independent variable). Removing of two outliers shown in the Bland Altman plot (Figure 1A) did not have any effect on the limits of agreement or the linear regression (data not shown). Therefore, they were included in further analyses. The Spearman`s rho of the MVPA was insignificant and weak (rho= 0.08, p=

0.509) for the NORDIET-FFQ, indicating that the questionnaire was not able to rank individual time in MVPA. Likewise, in the HUNT-PAQ, ranking of individual time in MVPA was also poor (Spearman`s rho of 0.14, p= 0.238). The NORDIET-FFQ captured 63% individuals fulfilling the recommendation of MVPA (specificity), whereas only 29% of those in need of PA counselling (sensitivity) (Table 3). The HUNT-PAQ was better at capturing individuals not fulfilling the recommendation of MVPA (sensitivity of 71%), but worse in identifying those who did (specificity of 36%).

//Table 3 placed here//

Moderate intensity physical activity recorded from the NORDIET-FFQ, HUNT- PAQ and SWA

Time spent in activity of moderate intensity PA (MPA) did not differ significantly by sex between the NORDIET-FFQ and SWA, whereas in HUNT-PAQ time in MPA was measured significantly different from SWA on group level (Table 2).

MPA was under-reported in both questionnaires as shown by the mean differences and limits of agreement from the Bland-Altman plots of -83 ± 512 min/week and -153 ± 523 min/week from the NORDIET-FFQ and HUNT-PAQ, respectively (Figure 1 B and E). The differences of MPA were randomly and evenly distributed above and below the mean difference for both questionnaires compared to SWA up to about 250 and 200 min/week with the NORDIET-FFQ and HUNT-PAQ, respectively (Figure 1 B and E). Linear regression also revealed a significant systematic under-reporting at higher levels of PA (MPA from SWA as independent variable) in both questionnaires (β=-0.78, $p<0.001$(NORDIET-FFQ) and β= -0.83, $p<0.001$ (HUNT-PAQ)).

Ranking of individual time in MPA was fair among women only (Spearman`s rho= 0.37, p= 0.027) with the HUNT-PAQ, but weak and insignificant with the NORDIET-FFQ (Spearman`s rho= 0.01, p= 0.402). The HUNT-PAQ captured 74% of individuals not fulfilling the recommendation of MPA (sensitivity), but only 36% of those who did (specificity). Both sensitivity and specificity for MPA were low with the NORDIET-FFQ (Table 3).

Vigorous intensity physical activity recorded from the NORDIET-FFQ, HUNT- PAQ and SWA

Median time in activity at vigorous intensity PA (VPA) was reported significantly differently between both questionnaires and SWA. The Bland Altman plot for VPA revealed an over-reporting of 36 ± 176 min/week (mean difference ± limits of agreement) with the NORDIET-FFQ, which increased with increased activity (Figure 1 C). Since only one participant reported VPA with the HUNT-PAQ, data from this activity are not presented. Moreover, the NORDIET-FFQ identified 75% of the individuals not fulfilling VPA.

Sedentary time recorded from the HUNT- PAQ and SWA

Amount of sedentary time was only measured in the HUNT-PAQ. Median time in sedentary intensity was significantly different between the questionnaire and SWA (Table 2). The Bland Altman plot revealed a high under-reporting of about 52% (6.5 h/day) compared to SWA, which decreased with increased sedentary time (Figure 1 F). However, the questionnaire was able to rank individuals according to sedentary time among women (r= 0.36. p= 0.035), but not among men or all participants in total.

Adherence to the recommendations of physical activity NORDIET-FFQ and HUNT-PAQ

Looking at each method separately, participants who reported to fulfil the MVPA of at least 150 minutes per week were 66% and 33% with the NORDIET-FFQ and HUNT-PAQ, respectively. However, only 55% of the participants actually met this recommendation according to the SWA (Table 4).

//Table 4 placed here//

Discussion

In the present study, we evaluated the ability of the questionnaires, NORDIET-FFQ and HUNT-PAQ, to estimate adherence to PA recommendations among CRC patients participating in the ongoing intervention, CRC-NORDIET study [38].

Generally, self-reported measures tend to over-report both duration and level of PA compared to objective methods [54], but under-reporting has also frequently been documented [54, 55] which may have several different explanations. A review of studies focusing on the comparison of objective measures versus self-reporting of PA was performed by Prince *et al.* [54]. They found that self-reported measures of PA were higher than the objective measure when accelerometers were used. However, in the present study MVPA (only HUNT-PAQ) and MPA were under-reported with the questionnaires compared to SWA. This may be for several reasons; firstly, the intensity level of MPA was defined as activities resulting in slight breathlessness. Cancer patients undergoing disease-related treatment and in a recovery phase post-surgery might experience breathlessness at lighter intensity than before, due to treatment effects and comorbidities such as anaemia, chronic obstructive pulmonary disease, and

physical deconditioning [56, 57]. Breathlessness may result in over-reporting of higher intensity (VPA) and under-reporting of MPA. Slightly reduced physical function, measured by handgrip-strength and 30-second sit-to-stand test, was observed in the CRC patients participating in the present study as compared to healthy individuals in Norway (Table 1) [58].

Secondly, the under-reporting of MPA might also be explained by the different techniques in recording physical activities used by the two methods. All activities are recorded by the SWA within a 24h day, whereas the questionnaires rely on the participant's memory and subjective evaluation of activity while responding to just a few questions [59].

Thirdly, the degree of under-reporting of MVPA and MPA was higher with the HUNT-PAQ than with the NORDIET-FFQ. This might be due to the restricted opportunity for the participants to report both MPA and VPA in the HUNT-PAQ, which is possible with the NORDIET-FFQ. Moreover, under-reporting may also be explained by the different reporting intervals of frequencies in the responses; the NORDIET-FFQ contained responses for activities lasting both less than and above 10-minutes intervals, while the HUNT-PAQ only asked for activities lasting more than 10-minutes intervals. Therefore, increased accuracy in reporting of intensities was possible with the NORDIET-FFQ compared to the HUNT-PAQ, since intensities performed for less than 10 minutes were not recorded with the HUNT-PAQ.

Bias in reporting of intensity seems to be influenced by the amount of questions for a specific activity within a questionnaire, i.e. whether it contains a single-item question or domain-item questions [60-63]. The self-reported sedentary time in the present study was based on a single-item question and was greatly under-reported by the HUNT-PAQ compared to SWA, an effect supported by other studies [60, 63]. Since the HUNT-PAQ asked for sedentary time during day-time, a general definition of a day in the SWA was performed by removing night-

hours between midnight and 6am. Consequently, sedentary time during day-time recorded by the SWA was calculated from 6am to midnight. However, this definition may be challenged in cancer patients facing several disease- and treatment side-effects influencing sleeping pattern due to increased need for resting time [64]. A diary report from each participant would probably improve the definition of night-time resulting in higher precision in reporting sedentary time during day-time.

Vassbakk- Brovold *et al.* [34] documented an over-reporting of 366% of MVPA recommendation with the short form International Physical Activity Questionnaire (IPAQ-sf) compared to the SWA among cancer patients undergoing chemotherapy. The IPAQ-sf contains 9 questions on PA [65], whereas the NORDIET-FFQ and HUNT-PAQ contains 2 and 4 questions on PA, respectively. Both questionnaires in the present study contained few detailed question about type of PA activities. Thus, under-reporting of the activities may be due to decreased precision in reporting different kinds of activities during a day. However, the number of questions depends on the rationale of the questionnaire. In the present study, the aim was to estimate adherence to the PA recommendations based on the Norwegian FBDG. In clinical practice as well as intervention studies, it is advantageous to have a short and easy PA assessment tool to be used when monitoring adherence to the PA recommendations.

A small mean difference of only 4% was revealed for MVPA by the NORDIET-FFQ, whereas HUNT-PAQ under-estimated by 58% compared to the SWA. This is comparable with previous studies, which have reported mean differences around 44% (ranging from -78% to 500%) [54]. Evenly distributed differences above and below the mean difference in the Bland Altman plots indicated no systematic bias of activities in any of the questionnaires.

However, linear regression revealed a systematic bias as shown by the significant negative slope for both questionnaires, indicating a trend towards more under-reporting with increased amount of PA. As can be seen from the Bland Altman plots, this negative trend seems to be accounted for by intensities higher than 250 and 200 min/week with the NORDIET-FFQ and HUNT-PAQ, respectively.

The limits of agreements were wide for both questionnaires, indicating weak ability to assess MVPA and MPA on an individual level. This has been supported by Ekelund *et al.* [66] and by Vassbakk- Brovold *et al*. [34], who validated the short form of the International Physical Activity Questionnaire (IPAQ-s) against an objective monitor among healthy Swedish adults and adult cancer patients, respectively. In the present study, limits of agreement were smaller at 150 min/week for MVPA and MPA for both questionnaires (about 500 min/week) than at higher levels of PA.

Hence, the NORDIET-FFQ was able to measure intensities up to about 250 min/week (i.e. including the PA recommendation of at least 150 min/week), but the HUNT-PAQ was less well suited to measure the corresponding intensities.

Studies including physical activities categorized in terms of different levels of exertion (light, moderate, vigorous) tend to result in more outliers, with VPA contributing the most outliers [54]. The present study reported more outliers at higher levels of all intensities, of which the more extreme differences in reporting tended to be among males. Importantly, there were few observations with high amounts of PA, indicating high uncertainty and low interpretation of those data.

Previous studies differ in degrees of correlation between self-reported methods and objective measurements of PA [54], with no specific trend. In the present study, there were poor

correlations for all variables between the NORDIET-FFQ and SWA, whereas fair correlations were found between the HUNT-PAQ and SWA for MPA and sedentary time among women only. Ranking of individuals according to time in MPA and sedentary time were thus fairly good with the HUNT-PAQ.

NORDIET-FFQ identified 63% of individuals fulfilling the MVPA (specificity), but was not able to identify those in need of PA counselling (sensitivity). However, the HUNT-PAQ was able to identify 71% not fulfilling the MVPA and 36% of those who did. Hence, the NORDIET-FFQ provided a fairly specific measure of PA, but limited sensitivity to correctly classify individuals not fulfilling the MVPA. Thus, NORDIET-FFQ should be used with care in a clinical setting. In contrast, the HUNT-PAQ was able to identify those in need of PA counselling, but limited in identifying those who fulfilled the PA recommendations.
About 66% reported meeting the recommended level of MVPA with the NORDIET-FFQ (i.e. 150 minutes/week) whereas 55% actually met the MVPA according to the SWA. This is comparable with Vassbakk- Brovold *et al.* [34] who also documented a higher proportion (i.e. 90%) of cancer patients perceiving themselves as meeting the MVPA recommendation of 150 minutes/week, while less than 50% actually met the PA recommendations recorded with SWA. This compares with a normal adult population in Norway, in which one in five met the national PA recommendations (i.e. 30 minutes/day) [21]. Importantly, the physical activity assessment method used in the normal Norwegian population survey was different from the one used in the present study and the study of Vassbakk-Brovold et al. [34]. Several barriers to meet PA recommendations among cancer survivors have been documented, of which treatment- and disease-related factors are dominant [67, 68]. Consequently, cancer patients may feel breathlessness at lighter intensities than normal, as abovementioned, resulting in

over-reporting of PA. Thus, these considerations are important to bear in mind when using self-reported data on PA in cancer patients.

The main strength of the present study was the use of SWA as the objective reference method in evaluating self-reported PA from the two questionnaires. Additionally, there was high compliance with the protocols for both self-reporting PA and wearing time of SWA. The NORDIET-FFQ and the HUNT-PAQ asked for PA in recent weeks (i.e. the previous 1-2 months), whereas the SWA recorded PA the subsequent week. Since none of the patients in the present study underwent chemotherapy during the validation period (i.e. mean time since last treatment of 155 days), less variation due to treatment effect on physical activity was therefore assumed. The limitation in our study was the use of different cut-off points defining frequency and duration of PA, which might have caused misclassification into MVPA, MPA and VPA activities between the questionnaires and SWA. This should be borne in mind when comparing other studies, which use different methods for measuring levels of PA [21, 65].

Conclusions

There are many inherent limitations in using short questionnaires to assess PA as compared to objective monitors. Both NORDIET-FFQ and HUNT-PAQ may be useful in assessing adherence to physical activity recommendations in colorectal cancer patients. Neither of the questionnaires was valid for estimating VPA. However, it is important to be aware of the limitations when interpreting the results from these questionnaires. An objective monitor should be considered to be used when more accurate individual data on PA and sedentary time are needed.

List of abbreviations

CRC: colorectal cancer; NORDIET-FFQ: Norwegian dietary guidelines food frequency questionnaire; HUNT-PAQ: The Nord-Trøndelag Health Study Physical activity questionnaire; FFQ: food frequency questionnaire; TNM: tumor node metastasis; ICD: International classification of diseases and related health problems; SWA: SenseWear Armband Mini; MPA: moderate physical activity; VPA: vigorous physical activity; MVPA: moderate-to-vigorous intensity; PA: physical activity; MET: metabolic equivalent.

Ethics approval and consent to participate

The CRC-NORDIET study is carried out in accordance with the Helsinki Declaration and informed consent was obtained from all participants. The study was approved by the Regional Committees for Medical and Health Research Ethics (REC Protocol Approval 2011/836) and by the data protection officials at Oslo University Hospital and Akershus University Hospital. The study is registered on the National Institutes of Health Clinical Trials (www.ClinicalTrials.gov; Identifier: NCT01570010).

Consent for publication

Not applicable.

Availability of data and material

Anonymized data resulting from this study may be available upon request by corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HBH had the main responsibility for writing the manuscript. HBH, SB, IP, MZ, AJS, SKB, CH, SS, MHC and RB contributed to the conception and the design of the study, analysis and interpretation of the data and drafting of the manuscript. HBH, SB, IP, AJS and SKB contributed to acquisition of data. All authors contributed to the writing and approval of the final manuscript.

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Figure title and legend

Figure 1 Bland-Altman plots depicting the mean differences (NORDIET-FFQ minus SenseWear Armband (SWA) and HUNT-PAQ minus SWA) for physical activity in minutes per week; A. MVPA minutes/week, NORDIET-FFQ, B. moderate physical activity in bouts

of 10 minutes/week, NORDIET-FFQ; C. vigorous physical activity in bouts of 10 minutes per week, NORDIET-FFQ; D. MVPA minutes per week, HUNT-PAQ; E. moderate physical activity in bouts of 10 minutes/week, HUNT-PAQ; F. Sedentary time in hours/day, HUNT-PAQ. The solid line represents the mean, and the dashed lines represent the 1.96 SDs of the observations. Females denoted as ♀ and males denoted as ♂.

Additional file 2 Bland-Altman plots depicting the mean differences (NORDIET-FFQ minus SenseWear Armband (SWA)) for physical activity in minutes per week; A. total-moderate physical activity in minutes/week, B. total-vigorous physical activity, minutes/week. The solid line represents the mean, and the dashed lines represent the 1.96 SDs of the observations. Females denoted as ♀ and males denoted as ♂.

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760 **Table 1** Characteristics of all participants in total and stratified by men and women (mean

761 (SD)).

Variables	Total (n = 78)	Men (n = 42)	Women (n = 36)	p[a]
Age, years, mean (SD)	64.8 (7)	65.2 (7.4)	64.3 (7.4)	0.590
Smokers, n (%)	6 (7.7 %)	3 (7 %)	3 (8 %)	1.000
EE, kJ/d[b], mean (SD)	10378 (1909)	11496 (1474)	9074 (1488)	<0.001
Education, n (%) (total n=78, men n=42, women n=36)				
Primary school	4 (5)	3 (7)	1 (3)	0.370
Lower secondary/High school	34 (44)	21 (50)	13 (36)	
College/University	40 (51)	18 (43)	22 (61)	
Anthropometry (mean, SD) (total n=78, men n=42, women n=36)				
Weight, kg	79.2 (16.3)	87.0 (11.9)	70.0 (16.1)	<0.001
Height, m	1.73 (8.31)	1.77 (6.7)	1.66 (5.3)	<0.001
BMI, kg/m^2	26.1 (5)	27.5 (3.7)	25.2 (5.5)	0.030
Waist circumference	93.9 (13.7)	100.7 (9.6)	86.2 (13.8)	<0.001
Hip circumference	101.0 (9.2)	101.6 (6.9)	100.3 (11.4)	0.560
Tumor classification n (%) (total n=70, men n=36, women n=34)				
TNM I	13 (17)	9 (25)	4 (12)	0.170
TNM II	33 (42)	18 (50)	15 (44)	
TNM III	24 (31)	9 (25)	15 (44)	
Physical performance (mean, SD) (total n=78, men n=42, women n=36)				
Hand-grip strength right, kg[c]	34.3 (9.5)	40.9 (6.6)	26.7 (5.9)	<0.001
Hand-grip strength left, kg[c]	31.1 (9.7)	37.9 (7.1)	23.5 (5.7)	<0.001
Sit-to-stand test	17.3 (5.3)	17.9 (5.8)	16.5 (4.6)	0.220

762 [a] Continuously variables were tested with Student t-test. Categorical variables were tested by the Fischer exact

763 test (two-sided).

764 [b] Estimated energy expenditure from the physical activity monitor SenseWear Armband Mini (BodyMedia,

765 Pittsburgh, Pennsylvania, USA) (SWA).

766 [c] The maximal strength of hand grip (kg) was recorded. For women and men, a 40 kg- and 80 kg-spring was

767 used, respectively.

768

769 TNM, Tumor Node Metastases; BMI, body mass index; EE, energy expenditure

Table 2 Physical activities and sedentary time, all participants in total and stratified by sex

	NORDIET-FFQ			SWA			NORDIET-FFQ/SWA p-values[b]		
Physical activity (min/week)[a]	Total (n =78) Median (P_5, P_{95})	Men (n=42) Median (P_5, P_{95})	Women (n=36) Median (P_5, P_{95})	Total (n = 78) Median (P_5, P_{95})	Men (n=42) Median (P_5, P_{95})	Women (n=36) Median (P_5, P_{95})	p_{tot}	p_{male}	p_{female}
MVPA	247 (0,691)	226 (0,812)	247 (0,641)	187 (12,881)	200 (2,1342)	169 (24,615)	0.897	0.759	0.838
MPA	152 (0,469)	159 (0,469)	152 (0,469)	187 (12,691)	200 (2,872)	169 (11,615)	0.007	0.050	0.090
VPA	0 (0,219)	0 (0,256)	0 (0,236)	0 (0,42)	0 (0,44)	0 (0,43)	<0.001	0.011	0.005
	HUNT-PAQ			SWA			HUNT-PAQ/SWA p-values[b]		
	Total (n=77)	Men (n=42)	Women (n=35)	Total (n=77)	Men (n=42)	Women (n=35)	p_{tot}	p_{male}	p_{female}
MVPA	72 (0,504)	38 (0,504)	113 (0,389)	182 (11,881)	200 (2,1342)	156 (23,618)	<0.001	<0.001	0.001
MPA	55 (0,504)	38 (0,504)	113 (0,353)	182 (11,696)	200 (2,872)	156 (11,618)	<0.001	<0.001	0.002
Sedentary time (h/day)	6 (0,12)	6 (0,13)	7 (0,12)	13 (10,15)	13 (10,15)	13 (10,15)	<0.001	<0.001	<0.001

[a] Physical activity levels based on Norwegian Food Based Dietary Guidelines

[b] Wilcoxon signed rank test, p-values for median physical activity from NORDIET-FFQ, HUNT-PAQ and SWA, both total and between sex

NORDIET-FFQ, Norwegian Dietary Guidelines Food Frequency Questionnaire; HUNT-PAQ, HUNT Physical Activity Questionnaire; SWA, SenseWear Armband; MVPA= (moderate physical activity 10 min bouts + (vigorous physical activity 10 min bouts*2)); bouts of 10 minutes=sum of at least 10 consecutive minutes of activity and above; MPA, moderate physical activity in bouts of 10 minutes; VPA, vigorous physical activity in bouts of 10 minutes.

Table 3 Sensitivity and specificity of the NORDIET-FFQ and HUNT-PAQ to detect participants not fulfilling or fulfilling the recommendations of physical activity relative to SWA.

	Sensitivity n[a] (%)		Specificity n[b] (%)	
Physical activity intensity	NORDIET-FFQ	HUNT-PAQ	NORDIET-FFQ	HUNT-PAQ
MVPA>150 min/week	10 (29)	25 (71)	27 (63)	15 (36)
MPA>150 min/week	16 (46)	26 (74)	22 (51)	15 (36)
VPA>75 min/week	57 (75)	-	0 (0)	0 (0)

[a] subjects reported not fulfilling the recommendations for both the NORDIET-FFQ/HUNT-PAQ and SWA

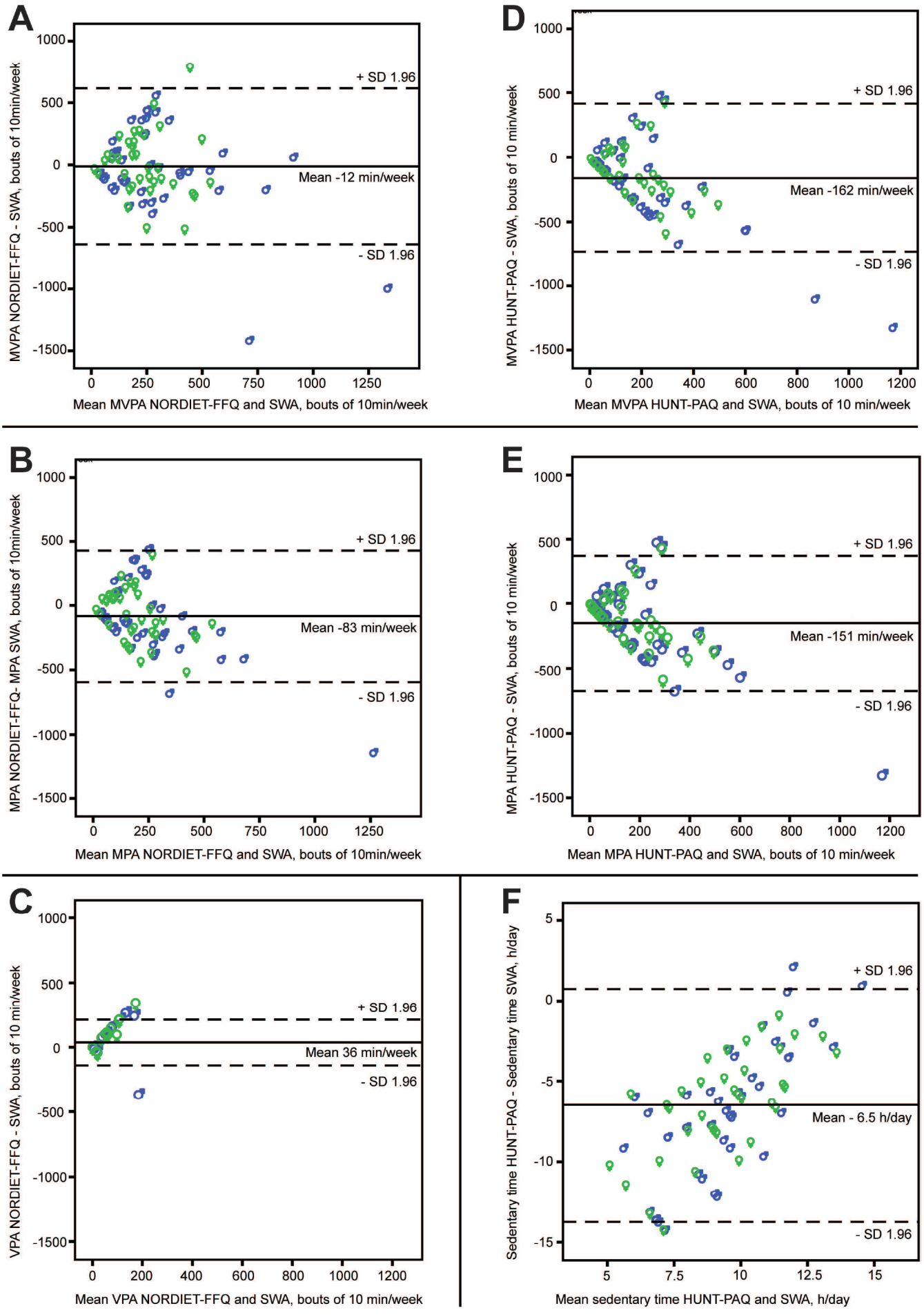
[b] subjects reported fulfilling the recommendations for both the NORDIET-FFQ/HUNT-PAQ and SWA

NORDIET-FFQ, NORDIET Food Frequency Questionnaire; HUNT-PAQ, HUNT Physical Activity Questionnaire; SWA, SenseWear Armband; MVPA=(moderate physical activity 10 min bouts + (vigorous physical activity 10 min bouts*2)); bouts=sum of at least 10 consecutive minutes of activity and above; MPA, moderate physical activity in bouts of 10 minutes; VPA, vigorous physical activity in bouts of 10 minutes.

Table 4 Proportion of participants (n (%)) reported to fulfil guideline of at least 150 minutes per week in MPA and MVPA in each measuring method

Recommendations of physical activity intensity	NORDIET-FFQ (n=78)	HUNT-PAQ (n=77)	SWA (n=78)
MVPA > 150 min/week	52 (66.7 %)	25 (32.5%)	43 (55.1 %)
MPA > 150 min/week	41 (52.6%)	24 (31.2)	43 (55.1%)

NORDIET-FFQ, NORDIET Food Frequency Questionnaire; HUNT-PAQ, HUNT Physical Activity Questionnaire;SWA, SenseWear Armband Mini; MVPA=(moderate physical activity 10 min bouts + (vigorous physical activity 10 min bouts*2)); bouts=sum of at least 10 consecutive minutes of activity and above; MPA, moderate physical activity in bouts of 10 minutes; VPA, vigorous physical activity in bouts of 10 minutes.


A
MVPA NORDIET-FFQ - SWA, bouts of 10min/week
+ SD 1.96
Mean -12 min/week
- SD 1.96
Mean MVPA NORDIET-FFQ and SWA, bouts of 10min/week
D
MVPA HUNT-PAQ - SWA, bouts of 10 min/week
+ SD 1.96
Mean -162 min/week
- SD 1.96
Mean MVPA HUNT-PAQ and SWA, bouts of 10 min/week
B
MPA NORDIET-FFQ- MPA SWA, bouts of 10min/week
+ SD 1.96
Mean -83 min/week
- SD 1.96
Mean MPA NORDIET-FFQ and SWA, bouts of 10min/week
E
MPA HUNT-PAQ - SWA, bouts of 10 min/week
+ SD 1.96
Mean -151 min/week
- SD 1.96
Mean MPA HUNT-PAQ and SWA, bouts of 10 min/week
C
VPA NORDIET-FFQ - SWA, bouts of 10 min/week
+ SD 1.96
Mean 36 min/week
- SD 1.96
Mean VPA NORDIET-FFQ and SWA, bouts of 10 min/week
F
Sedentary time HUNT-PAQ - Sedentary time SWA, h/day
+ SD 1.96
Mean - 6.5 h/day
- SD 1.96
Mean sedentary time HUNT-PAQ and SWA, h/day

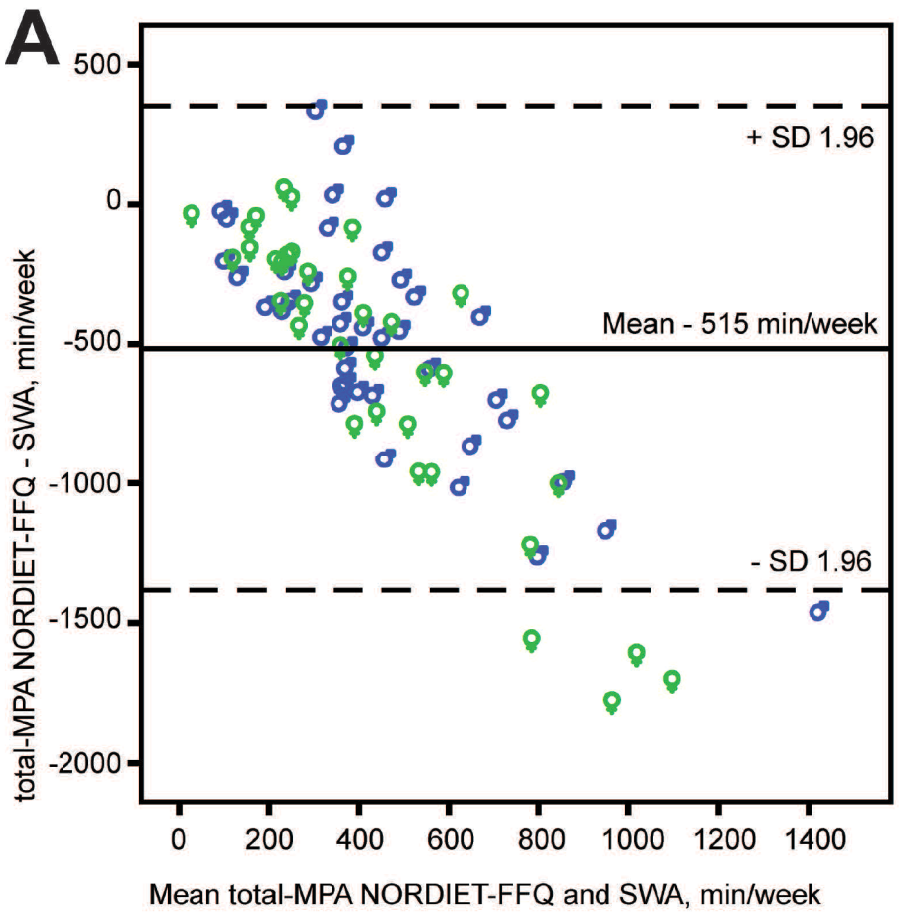
Additional file 1 Physical activity, all participants in total and stratified by sex

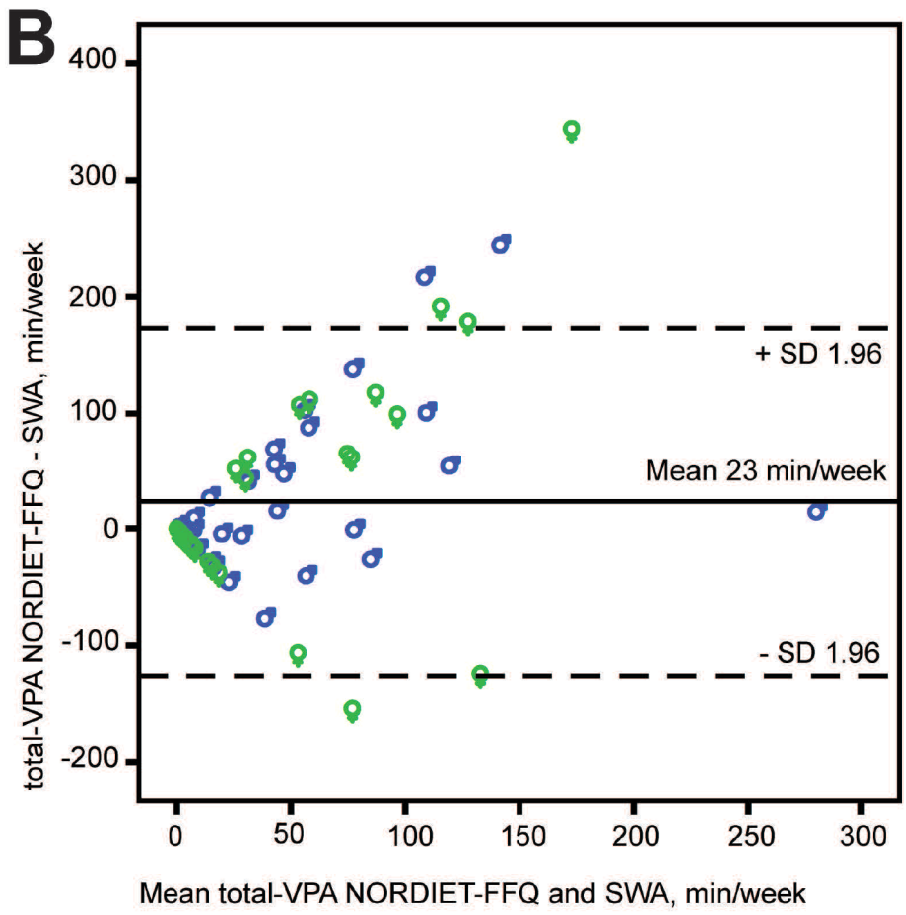
Physical activity (min/week)[a]	NORDIET-FFQ			SWA			NORDIET-FFQ/SWA p-values[b]		
	Total (n =78)	Men (n=42)	Women (n=36)	Total (n = 78)	Men (n=42)	Women (n=36)	p_{tot}	p_{male}	p_{female}
	Median (P_5, P_{95})	Median (P_5, P_{95})	Median (P_5, P_{95})	Median (P_5, P_{95})	Median (P_5, P_{95})	Median (P_5, P_{95})			
total-MPA	152 (0, 469)	159 (0, 469)	152 (7, 469)	629 (135, 1823)	646 (133, 1519)	607 (169, 1866)	<0.001	<0.001	0.001
total-VPA	0 (0, 219)	4 (0, 256)	0 (0, 236)	8 (0, 109)	9 (0, 97)	6 (0, 160)	0.082	0.245	0.202

[a]Physical activity levels based on Norwegian Food Based Dietary Guidelines

[b] Wilcoxon signed rank test, p-values for mean physical activity from NORDIET-FFQ and SWA, both total and between sex

NORDIET-FFQ, Norwegian Dietary Guidelines Food Frequency Questionnaire;SWA, SenseWear Armband; total-MPA= total moderate physical activity; total-VPA=total vigorous physical activity


A
500
0
-500
-1000
-1500
-2000
+ SD 1.96
Mean - 515 min/week
- SD 1.96
total-MPA NORDIET-FFQ - SWA, min/week
0
200
400
600
800
1000
1200
1400
Mean total-MPA NORDIET-FFQ and SWA, min/week


B
400
300
200
100
0
-100
-200
+ SD 1.96
Mean 23 min/week
- SD 1.96
total-VPA NORDIET-FFQ - SWA, min/week
0
50
100
150
200
250
300
Mean total-VPA NORDIET-FFQ and SWA, min/week

10 Supplementary files 1-4

Supplementary file 1

Typisk Norsk-studien

SPØRRESKJEMA OM DE SISTE UKENES KOSTHOLD OG FYSISK AKTIVITET

Vi ønsker opplysninger om ditt vanlige kosthold du har hatt de siste 1-2 måneder.

Skjemaet skal leses av en maskin og det er derfor viktig at du setter tydelige kryss i rutene. Bruk blå eller sort kulepenn. Alle svar vil behandles fortrolig.

Riktig markering i rutene er slik: [X]
Ved feil markering, fyll hele ruten slik: ■

Av hensyn til den maskinelle lesningen - pass på at arkene ikke brettes. Har du spørsmål angående utfyllingen av skjemaet kan du ringe:
Hege Berg Henriksen på prosjekttelefon: 932 00 727

V3/V4

Fornavn, mellomnavn:_____

Etternavn: _____

1. GENERELLE OPPLYSNINGER

1a **Kjønn** Mann ☐ Kvinne ☐ **Alder** ☐☐ år **Høyde** ☐☐☐ cm **Vekt:** ☐☐☐ kg

2. FRUKT OG BÆR

		Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang				
		0	1	2	3	4	5	6-7	8+					
2a	Stor frukt (f.eks. et helt eple, nektarin, banan, appelsin, en skive melon o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
2b	Mellomstor frukt (f.eks. klementiner, kiwi, plommer o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
2c	Liten frukt (f.eks druer o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-10 ☐	11-20 ☐	21-40 ☐	41+ ☐
2d	Bær (ferske og frosne jordbær, blåbær, bringebær, tyttebær, kirsebær o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐
2e	Tørket frukt (f.eks. rosiner, aprikos, svisker, epler, ferdige blandinger o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐

3. NØTTER

		Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang				
		0	1	2	3	4	5	6-7	8+					
3a	Usaltede nøtter (f.eks. mandler, peanøtter, valnøtter, cashew, ferdig blandinger o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(neve= 25g)	1/2 ☐	1 ☐	2 ☐	3+ ☐
3b	Saltede nøtter (f.eks. peanøtter, valnøtter, ferdige blandinger, chilinøtter, pekannøtter, mandler o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(neve= 25g)	1/2 ☐	1 ☐	2 ☐	3+ ☐

4. GRØNNSAKER (ikke potet)

		Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang						
		0	1	2	3	4	5	6-7	8+							
4a	Hvitløk (friske, hermetiske)	☐	☐	☐	☐	☐	☐	☐	☐	(fedd=båt)	1/4 ☐	1/2 ☐	1 ☐	2 ☐	3+ ☐	
4b	Løk, vårløk og purre	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
4c	Tomat (friske, 6 cherry= 1 vanlig tomat)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3 ☐	4+ ☐	
4d	Tomatsaus (inkludert ketchup, tomatpure)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/4 ☐	1/2 ☐	1 ☐	2 ☐	3+ ☐	
4e	Blandet salat (f.eks. bladsalat, paprika, agurk, mais o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(liten bolle=100g)	1/4 ☐	1/2 ☐	1 ☐	2 ☐	3+ ☐	
4f	Andre grønnsaker (f.eks. gulrot, brokkoli, blomkål,kålrot, hodekål, frosne blandinger o.l)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	

5. KORN

		Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr. gang					
		0	1	2	3	4	5	6-7	8+						
5a	Søtet frokostblanding (f.eks.Corn Flakes, Chocofrokost o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐	
5b	Usøtet frokostblanding eller grøt (f.eks. havregrøt, 4-Korn o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐	

6. DRIKKE

		Hvor mange ganger pr. uke drakk du								Hvor mye drakk du pr.gang						
		0	1	2	3	4	5	6-7	8+							
6a	Vann (springvann, flaskevann)	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐
6b	Annen drikke uten tilsatt sukker (f.eks. farris, lettsaft, lettbrus o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐
6c	Juice (f.eks. eplejuice, appelsinjuice, Manajuice o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐
6d	Annen drikke tilsatt sukker (f.eks. brus, saft, nektar o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐
6e	Lettmelk, ekstra lettmelk, skummet melk o.l.	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐
6f	Helmelk, kefir, kulturmelk o.l.	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐
6g	Øl med alkohol	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐
6h	Vin med alkohol	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐
6i	Brennevin	☐	☐	☐	☐	☐	☐	☐	☐	(glass)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐
6j	Kaffe (filterkaffe)	☐	☐	☐	☐	☐	☐	☐	☐	(kopp)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐
6k	Annen kaffe (f.eks. espresso,presskanne,kapsel o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(kopp)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐
6l	Te (f.eks. svart, grønn, urtete o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(kopp)	1/2 ☐	1 ☐	2 ☐	3-4 ☐	5-6 ☐	7+ ☐

7. KAKER, DESSERT, GODTERI

		Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang						
		0	1	2	3	4	5	6-7	8+							
7a	Kaker, hvetebakst, vafler, søt kjeks	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
7b	Dessert (f.eks. is, hermetisk frukt, pudding)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐	
7c	Sjokolade, godteri	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon =100g)	1/4 ☐	1/2 ☐	1 ☐	1 1/2 ☐	2+ ☐	
7d	Potetgull, chips	☐	☐	☐	☐	☐	☐	☐	☐	(neve)	1-2 ☐	3-5 ☐	6-8 ☐	9-11 ☐	12+ ☐	

8. BRØD (f.eks. 1/2 rundstykke = 1 skive, 1 baguett = 4 skiver, 1 ciabatta = 2 skiver)

		Hvor mange skiver spiste du pr. DAG													
		0	1/2	1	2	3	4	5	6	7	8	9	10	11	12+
8a	Fint brød, 0-25% sammalt mel (f.eks. loff, baguetter, fine rundstykker, ciabatta)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8b	Halvgrovt brød, 25-50% sammalt mel (f.eks. helkornbrød, kneipp, grove rundstykker)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8c	Grovt brød, 50-75% sammalt mel (f.eks. havrebrød)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8d	Ekstra grovt brød, 75-100% sammalt mel (f.eks. mørkt rugbrød)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8e	Fint knekkebrød (f.eks. kavring, frokost knekkebrød)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8f	Grovt knekkebrød (f.eks. Husmann, Sport, Solruta o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Sum skiver pr.dag=_____ Antall skiver pr.uke:_____x 7=_____. Tallet brukes i spørsmål 9.
(sum skiver pr.dag)

9. REGISTRER PÅLEGGET DU VANLIGVIS SPISER PÅ DISSE SKIVENE I LØPET AV EN UKE:

		Antall skiver pr. UKE									
		0	1	2-3	4-5	6-7	8-12	13-18	19-24	25-30	31+
9a	Fete oster som pålegg (f.eks. helfet Norvegia, helfet Jarlsberg, brie o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9b	Magre oster som pålegg (f.eks. lett Norvegia, lett Jarlsberg, cottage cheese o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9c	Fiskepålegg (f.eks. makrell i tomat, røket/gravet laks, sild o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9d	Rødt kjøtt (f.eks. salami, skinke, servelat, leverpostei, roastbiff o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9e	Hvitt kjøtt (f.eks. kyllingpålegg, kalkunpålegg, kyllingleverpostei o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9f	Pålegg med sukker (f.eks honning, syltetøy, nøttepålegg o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9g	Grønnsaker og frukt som pålegg (f.eks. paprika, agurk, avokado, banan, eple o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

10. Hvilken type smør/margarin/olje brukte du oftest til:

	NB! Sett **ETT** kryss på hver linje	Bruker ikke	Mykt margarin (Soft Flora, Vita, Soft oliven)	Hardt smør (meierismør, Bremykt, Melange)	Oljer (olivenolje, soyaolje, rapsolje, Vita hjertego)
10a	Matlaging, steking, baking	☐	☐	☐	☐
10b	På brød, baguette, rundstykke	☐	☐	☐	☐

11. MEIERIPRODUKTER

		Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr. gang						
		0	1	2	3	4	5	6-7	8+		1/4	1/2	1	1 1/2	2	3+
11a	Meieriprodukter med høyt fettinnhold (f.eks. seterrømme, creme fraiche, yoghurt o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	☐	☐
11b	Magre meieriprodukter (f.eks. ekstra lettrømme, mager kesam, lett yoghurt o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	☐	☐

12. FISK TIL MIDDAG/VARM LUNSJ

		Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr. gang						
		0	1	2	3	4	5	6-7	8+		½	1	2	3	4	5+
12a	Fet fisk til middag (f.eks. laks, ørret, sild, kveite o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon= 145g)	☐	☐	☐	☐	☐	☐
12b	Mager fisk (f.eks. torsk, sei, hyse, rødspette, breiflabb o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon= 145g)	☐	☐	☐	☐	☐	☐
12c	Bearbeidet fisk (f.eks.fiskegrateng, fiskepudding, fiskeboller, fiskegryte o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon= 180g)	☐	☐	☐	☐	☐	☐

13. KJØTT TIL MIDDAG/VARM LUNSJ

		Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang						
		0	1	2	3	4	5	6-7	8+		½	1	2	3	4	5+
13a	Rent rødt kjøtt (storfe, svin, sau/lam eller geit)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon =150g)	☐	☐	☐	☐	☐	☐
13b	Bearbeidet rødt kjøtt (f.eks. kjøttdeig, pølser, hamburger, kjøttboller o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon =150g)	☐	☐	☐	☐	☐	☐
13c	Rent hvitt kjøtt (f.eks. kylling, høne, kalkun o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon =150g)	☐	☐	☐	☐	☐	☐
13d	Bearbeidet hvitt kjøtt (f.eks. pølser, kjøttboller, hamburger o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(porsjon =150g)	☐	☐	☐	☐	☐	☐

14. RIS OG PASTA

		Hvor mange ganger pr. uke spiste du								Hvor mye spiste du pr.gang				
		0	1	2	3	4	5	6-7	8+		1	2	3	4+
14a	Polert, hvit ris	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
14b	Upolert, naturris	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
14c	Vanlig pasta	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
14d	Fullkornspasta	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐

15. KOSTTILSKUDD (ts = teskje, bs = barneskje, ss=spiseskje)

		Hvor mange ganger pr. uke spiste du								Hvor mye tok du pr. gang				
		0	1	2	3	4	5	6-7	8+		1 ts	1 bs	1 ss	
15a	Tran	☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	
15b	Trankapsler, Fiskeoljekapsler, omega-3 tilskudd	☐	☐	☐	☐	☐	☐	☐	☐	(kapsler)	1 ☐	2 ☐	3 ☐	4+ ☐
15c	Vitamin D	☐	☐	☐	☐	☐	☐	☐	☐	(piller)	1 ☐	2 ☐	3 ☐	4+ ☐
15d	Multivitamin tilskudd	☐	☐	☐	☐	☐	☐	☐	☐	(piller)	1 ☐	2 ☐	3 ☐	4+ ☐

16. DAGLIG FYSISK AKTIVITET (Registrer hele treningsøkter og vanlig fysisk aktivitet i dagliglivet)

		Hvor mange ganger pr. uke var du fysisk aktiv								Hvor lenge var du fysisk aktiv pr. gang (minutter)							
		0	1	2	3	4	5	6-7	8+		1-4	5-9	10-15	16-20	21-30	31-45	46-60	60+
16a	Moderat intensitet (f.eks. hurtig gange, fysisk aktivitet i arbeid, hardt husarbeid, annen aktivitet der du blir lett andpusten)	☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐
16b	Høy intensitet (f.eks. jogging, skigåing, hard fysisk aktivitet i arbeid, driver trening/idrett, annen aktivitet der du blir veldig andpusten)	☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐

Supplementary file 2

Typisk Norsk-studien

Dato: _____

Visit: _____

IDnr: _____

SPØRSMÅL OM MOSJON/FYSISK AKTIVITET

Skjemaet skal leses av en maskin og det er derfor viktig at du setter tydelige kryss i rutene. Bruk blå eller sort kulepenn. Alle svar vil behandles fortrolig.

Riktig markering i rutene er slik: [X]

Ved feil markering, fyll hele ruten slik: ■

Av hensyn til den maskinelle lesningen - pass på at arkene ikke brettes. Har du spørsmål angående utfyllingen av skjemaet kan du ringe:

Hege Berg Henriksen eller Katrine Rolid på prosjekttelefon: 932 00 727

1. Hvor ofte driver du mosjon?

Med mosjon mener vi at du for eksempel går tur, går på ski, svømmer eller driver trening/idrett.

- ☐ Aldri
- ☐ Sjeldnere enn en gang i uka
- ☐ En gang i uka
- ☐ 2-3 ganger i uka
- ☐ Omtrent hver dag

2. Dersom du driver slik mosjon, så ofte som en eller flere ganger i uka; hvor hardt mosjonerer du? (Ta et gjennomsnitt)

- ☐ Tar det rolig uten å bli andpusten eller svett
- ☐ Tar det så hardt at jeg blir andpusten og svett
- ☐ Tar meg nesten helt ut

3. Hvor lenge holder du på hver gang? (Ta et gjennomsnitt)

- ☐ Mindre enn 15 minutter
- ☐ 15-29 minutter
- ☐ 30 minutter - 1 time
- ☐ Mer enn 1 time

4. Fysisk aktivitet i hverdagen

	Ja	Nei
Har du vanligvis minst 30 minutter fysisk aktivitet daglig på arbeid og/eller i fritida?	☐	☐

5. Stillesitting i hverdagen

Omtrent hvor mange timer sitter du i ro på en vanlig hverdag?
(Regn med både jobb og fritid)

☐☐

Supplementary file 3

Prosedyre

7-dagers veid kostregistrering

Forside: fyll ut **ID.nr**. og **registreringsperiode;** 4+3 dager evn. 7 dager i strekk (avtales med pasient på baseline-måledagen eller på første inspirasjonsmøte)

Veiledning kostdagbok

- deltaker bør spise som vanlig
- registrerer kosten i **7 dager**
- ny side for hvert måltid
- noter **dag, dato, klokkeslett**, **måltid**, **matvaretype og – mengde (g)** samt **tilberedningsmåte**
- eventuelle oppskrifter noteres bakerst i heftet
- husk å få med alt som blir spist/drukket: f.eks.: smør, godterier, fløte i kaffen…
- trekk fra det som ikke blir spist opp: f.eks.: epleskrott, bananskall, rester på tallerkenen

Vekt /veiing

- Vis deltaker vekten og hvordan den brukes: ON/OFF, TARE=nullstilling, UNIT: benevningen skal stilles inn på gram (g).
- Eksempel på hvordan veie et sammensatt måltid:
    - sett asjetten på vekten og nullstill
    - legg på en matvare(f.eks brødskive), les av vekten, noter og nullstill
    - legg på neste matvare(f.eks smør/margarin), les av vekten, noter og nullstill osv.
    - dersom måltidet består av sammensatte retter som f.eks lapskaus, supper og lignende, veies hele retten i ett

Måltider spist borte

- Dersom problematisk å få veid; noter så nøyaktig som mulig hva som ble spist og mengder(dl, spiseskjeer, kopper, antall, str. etc.).

Drikke

- sett glass/kopp på vekten, nullstill, hell oppi det som skal drikkes og noter vekten

eller

- noter mengden i dl

UiO : Det medisinske fakultet

KOSTDAGBOK FOR
7 DAGERS VEID KOSTREGISTRERING

ID.NR:_____

REGISTRERINGSPERIODE 1:_____

REGISTRERINGSPERIODE 2:_____

Veiledning for 7 dagers veid registrering av kostholdet ditt

Spis slik du pleier å gjøre!

Prøv å ikke la kostregistreringen forandre eller påvirke ditt valg av matvarer. Dersom det skjer vil det føre til at vi får et galt bilde av kosten din.

- Registrer kosten din alle 7 dagene.
- Begynn med det første måltidet den dagen registreringen starter.
- Bruk en ny side for hvert måltid
- Registreringen avsluttes med det siste måltidet som blir spist den siste dagen av registreringen.

Her er et eksempel på hvordan du fyller ut kostdagboken:

Frokost ☐ **Lunsj** ☐ **Middag** ☒ **Kvelds** ☐ **Mellommåltid** ☐

Dag og dato: 24.april 2006 Kl. 17.15 Hvor spist:… hjemme……

Skal ikke fylles ut!

Matvare/rett/drikke/produktnavn	**Mengde**	Kode	Mengde
Kokte poteter	215 g		
Kjøttkaker, Prior kjøttboller, stekt	138 g		
Kokt brokkoli	104 g		
Kokte gulerøtter	68 g		
Brun saus fra Toro	73 g		
2 glass vann	342 g		

Når registreringsperioden er over, sender du den ferdig utfylte kostdagboken tilbake til oss i den frankerte returkonvolutten.

Takk for at du har tatt deg tid til å delta. Ved å veie og registrere kosten din denne uken bidrar du til ny kunnskap om kostholdet i den norske befolkningen.

Frokost ☐ **Lunsj** ☐ **Middag** ☐ **Kvelds** ☐ **Mellommåltid** ☐

Dag og dato: _____ **Kl.** _____ **Hvor spist:** _____ .

Skal ikke fylles ut.

Matvare/rett/drikke/produktnavn	**Mengde**	Kode	Mengde

Oppskrift:.....

Når spist, dato og måltid:.....

Ingrediens:	**Mengde**	Skal ikke fylles ut. Kode	Mengde

Supplementary file 4

UNIVERSITETET I OSLO
DET MEDISINSKE FAKULTET

Deltaker-Brukerveiledning for Armband

SenseWear Armband Mini (model MF-SW)

Når må ikke Armband benyttes

- Ved kjent metallallergi, eksem eller lett irritabel hud
- Under strålebehandling
- Dersom du har pacemaker
- Sammen med annet utstyr som kan forårsake elektromagnetiske forstyrrelser (i fly, på sykehus, ved bruk av pulsklokke osv…)

Bruk av Armband

Hvordan ha den på:

- Festes på baksiden av venstre overarm (triceps), Armband-logoen skal peke oppover mot skulderen og sølv-sensorene på undersiden av Armband skal være i kontakt med huden. Overarmen skal være ren, tørr og uten krem/olje ol. Stroppen strammes så den sitter komfortabelt, men stramt nok så Armband ikke sklir nedover armen, det skal være plass til to fingre under stroppen.
- Brukes **7 dager** i strekk: **23t/døgn** med 1 time hvor den er tatt av.
- Armband slår seg PÅ automatisk og begynner å lagre data innen 10 min etter at den er tatt på armen, Aktiveringen indikeres av en rekke lyd-toner (det er ingen AV- og PÅ knapp
- *Når armband kan benyttes*: når deltakeren sover, trener og ellers ved daglige rutiner.
- *Når Armband ikke kan benyttes*: I dusjen eller på svømming – **tåler ikke vann!!!**

Renhold:

Rengjør Armband etter å ha svettet eller dersom den blir synlig skitten.

- *Rengjøring av Armband:*

(**NB**: husk først å separere Armband fra stroppen: med Armband-logoen pekende oppover, press den hvite delen av Armband ut av den grå delen som stroppen henger fast i.)
Den siden som berører huden tørkes av med en fuktig klut med mild såpe, sørg deretter for å fjerne såperester og tørk til slutt med en tørr klut

- *Rengjøring av Armband-stroppen:* vaskes for hånd med en mild såpe i varmt vann, skylles og luft-tørkes.
- *Desinfisering:* Armband skal alltid desinfiseres før den skal brukes av nye deltakere. Tørk over Armband med en myk klut fuktet med 70 % isopropyl alkohol. La Armband tørke 5-10 minutter før den brukes.

Opplading:

- Lades opp ved bruk av USB-kabel (følger med), som koples til PC. Fullstendig oppladning tar ca. 3 timer. Batteriet har varighet 5-7 dager. (Batteri-lysindikatorer: grønn: mer enn 24 t igjen, orange: mindre enn 24t igjen, rød: trengs oppladning umiddelbart)

! Farer ved bruk

- Hudirritasjon (rapportert hos < 1 % av brukerne) Viktig å følge rådene for hvordan Armband skal regngjøres og festes rundt armen. Hvis hudirritasjonen skulle vedvare – avslutt bruken av Armband og eventuelt konsulter med fastlegen.

Husk å tilbakesende Armband i medfølgende returkonvolutt etter avsluttet bruk!

Takk ☺