The importance of dietary factors in knee osteoarthritis

an evidence-based approach

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THE IMPORTANCE OF DIETARY FACTORS IN KNEE OSTEOARTHRITIS

- An Evidence-Based Approach

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PREFACE

The present thesis is based on the four papers listed below (I – IV). All studies have been carried out at the Parker Institute, Frederiksberg Hospital, in collaboration with the Department of Human Nutrition, Faculty of Life Sciences, University of Copenhagen.

I:

Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. ***Osteoarthritis and Cartilage*** 2005; 13(1):20-27.
doi:10.1016/j.joca.2004.10.008

II:

Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. ***Annals of the Rheumatic Diseases*** 2007; 66(4):433-439.
doi: 10.1136/ard.2006.065904

III:

Christensen R, Bartels EM, Astrup A, Bliddal H. Symptomatic efficacy of avocado/soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials. ***Osteoarthritis and Cartilage*** 2008; 16(4):399-408.
doi:10.1016/j.joca.2007.10.003

IV:

Christensen R, Bartels EM, Altman RD, Astrup A, Bliddal H. Does the hip powder of *Rosa canina* (rosehip) reduce pain in osteoarthritis patients? - A meta-analysis of randomized controlled trials. ***Osteoarthritis and Cartilage*** 2008; 16(9):965-72.
doi:10.1016/j.joca.2008.03.001

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From Canada, I would like to thank Professor Peter Tugwell (Centre for Global Health, Institute of Population Health, University of Ottawa) & Professor George A. Wells, MSc, PhD (University of Ottawa Heart Institute) for including me as statistical editor in CMSG - as well as inviting me to join OMERACT as a biostatistician. From The United States of America, I would like to thank Professor Roy D. Altman (Division of Rheumatology and Immunology at the University of

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The studies on which this thesis is based would have been impossible to perform without the generous financial support of ***The Oak Foundation*** and ***The Danish Rheumatism Association*** towards whom I am also very grateful. I acknowledge *Osteoarthritis and Cartilage* (ELSEVIER), and the *Annals of the Rheumatic Diseases* (BMJ Journals, BMJPG Ltd), for giving me permission to reprint my papers as part of this thesis.

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Thank You!

_____

Robin Christensen
Frederiksberg, Autumn 2008

INTRODUCTION

Hypotheses

The hypotheses of this PhD study were:

1. Non-pharmacological treatments of osteoarthritis (OA) may be handled and analysed as evidence-based as pharmacological therapy.
2. Weight loss is the most efficient non-pharmacological therapy in obese patients with knee OA.
3. A ranking of effect size for the dietary factors available can be extrapolated from available published studies – including meta-analyses.

Aims

To describe important non-pharmacological treatments of knee OA with special emphasis on the possible evidence of dietary treatments based on studies described in the literature and on our own experiments.

To apply the instruments for statistical evaluation of existing literature on non-pharmacological treatment in knee OA. To give a perspective of the importance of patients' self-care in the treatment of knee OA.

KNEE OSTEOARTHRITIS

Epidemiology, classification and diagnosis

WHO estimates that osteoarthritis (OA) affects 9.6% of men and 18% of women older than 60 years of age (1). Increases in life expectancy and ageing populations are expected to make OA the fourth leading cause of disability by the year 2020 (2). Knee OA is associated with symptoms of pain, functional disability, and joint morning stiffness which is not lasting longer than half an hour (3). The prevalence of radiological findings of knee OA is estimated to approximately 70% of an elderly population exceeding 65 years of age (4). Approximately 25% of subjects 55 years of age or older have had knee pain most days in a month in the past year (5). Around half of these subjects have *radiographic* OA in the knee and are considered to have *symptomatic* OA (3). Before the age of 50, men have a higher prevalence and incidence of OA than women, presumably due to secondary changes following trauma, while after the age of 50, women have both a higher prevalence and incidence (6).

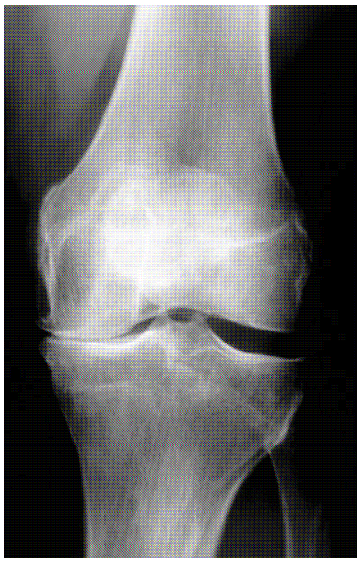

Figure 1:
Radiogram of the right knee of a patient with severe OA. OA leads to degenerative changes in cartilage, subchondral bone and the adjacent soft-tissue structures. In the knee joint, radiograms are taken with the patient standing, i.e. weight bearing. It is evident from this radiogram that the medial compartment of the knee is almost worn down with respect to cartilage, as seen by the loss of space between the bones. The implications for alignment of the joint are significant and with a surplus of weight in the obese patient, functional problems of such joint are multiplied.
(Bliddal & Christensen, *Obes. Rev.* 2006, 7: 323-331)

Yelin reviewed the cost of OA from previously published data (7), which were estimated in the US to be in the order of $15.52 billion (1994 dollars). This is about 2.8 times more than the estimated cost of rheumatoid arthritis (RA $5.56 billion). At least half of the OA cost is due to work loss (7). There is a significant genetic component in the prevalence of knee OA, with heritability estimates from twin studies between 39% and 65% independent of known environmental or demographic confounders (8). In general, physical disability arising from pain and loss of functional capacity reduces quality of life (9;10), and epidemiologic data supports that low physical activity increases the risk of further morbidity and mortality (11;12).

In the clinic, it is important to differentiate painful OA from three other causes of regional or generalised joint pain in older people: referred pain, peri-articular (soft-tissue) conditions, and somatisation (regional pain in the absence of any local pathological cause) (13). According to Dieppe and Lohmander, however, the main clinical features of OA make it, in general, an easily recognised clinical entity, with common clinical features that allow a bedside diagnosis of OA to be made (13):

- *Increased age*: It is unusual to develop the disease before the age of 40 years
- *Pain*: Use-related joint pain, relieved by rest, is one of the cardinal features of the disease. In more advanced cases, rest pain and night pain may also develop
- *Stiffness*: Most people with symptomatic OA of large joints experience short-lasting inactivity stiffness or gelling of joints, which wears off in a few minutes with use
- *Reduced movement*: The range of movement of the joint is often restricted, and there is generally pain with movement, particularly at the end of the range
- *Swelling*: Many OA joints develop palpable firm swellings at the joint margin due to the formation of osteophytes. Some have minor soft tissue swelling due to secondary synovitis
- *Crepitus*: OA joints often crack or creak on movement

Criteria for classification of symptomatic OA have been developed by a subcommittee of the American College of Rheumatology (ACR) (14). According to the ACR - for the purposes of classification - it should be specified whether OA of the knee is of unknown origin (idiopathic, primary) or is related to a known medical condition or event (secondary). Clinical criteria for the classification of idiopathic OA of the knee were developed through a multicenter study group (15): comparison diagnoses included rheumatoid arthritis and other painful conditions of the knee, exclusive of referred or para-articular pain. Variables from the medical history, physical examination, laboratory tests, and radiographs were used to develop sets of criteria serving different investigative purposes. The ‘1986 Criteria’ for classification of idiopathic OA of the knee are presented in **Table 1**.

Table 1:

ACR (1986) criteria for classification of idiopathic OA of the knee

Clinical and laboratory	**Clinical and radiographic**	**Clinical**†
Knee pain + at least 5 of 9:	Knee pain & Osteophytes + at least 1 of 3:	Knee pain + at least 3 of 6:
- Age > 50 years - Stiffness < 30 minutes - Crepitus	- Age > 50 years - Stiffness < 30 minutes - Crepitus	- Age > 50 years - Stiffness < 30 minutes - Crepitus
- Bony tenderness - Bony enlargement - No palpable warmth		- Bony tenderness - Bony enlargement - No palpable warmth
- ESR <40 mm/hour - RF <1:40 - SF OA		
92% sensitive 75% specific	91% sensitive 86% specific	95% sensitive 69% specific

*ESR = erythrocyte sedimentation rate (Westergren); RF = rheumatoid factor; SF OA = synovial fluid signs of OA (clear, viscous, or white blood cell count <2,000/mm^3).
†Alternative for the clinical category would be 4 of 6, which is 84% sensitive and 89% specific.

Altman et al. ***Arthritis Rheum*** 1986;29:1039-1049.

The pain of OA is usually related to activity. Thus, pain in the knee at night reflects either severe symptomatic disease or pain from causes other than OA, such as inflammatory arthritis, tumours, infection, or crystal disease (3). For OA of the knee, activities such as climbing stairs, getting out of a chair, and walking long distances, bring on pain. Morning stiffness usually lasts less than 30 minutes (15). A thorough examination of the patient must include testing for various possible causes of knee pain (3). As indicated in Table 1, no blood tests are routinely indicated in the assessment of a patient with chronic knee pain, unless symptoms and signs suggest rheumatoid arthritis or other forms of inflammatory arthritis (14). Examination of synovial fluid is indicated if inflammatory arthritis including gout or pseudo-gout is suspected, or if joint infection is a concern. A white-cell count below 1000 per cubic millimetre in the synovial fluid is consistent with OA, whereas higher white-cell counts suggest inflammatory arthritis. The presence of crystals is diagnostic of either gout or pseudo-gout (3).

Principles of management

The goals of the contemporary management of the patient with OA continue to include control of pain and improvement of function and health-related quality of life, with avoidance, if possible, of toxic effects of applied therapy (16). Treatment of OA involves alleviating pain, attempting to rectify mechanical mal-alignment, and identifying and addressing manifestations of joint instability (3). The *European League Against Rheumatism* (EULAR) has previously reviewed the multiple

treatment strategies in the management of OA of the knee and presented their recommendations following a combination of evidence-based medicine and expert opinion (17). According to the EULAR recommendations, the current types of treatment aiming at alleviating pain and disability may be categorised as: (*i*) Non-pharmacological treatment (e.g. education, exercise, lifestyle changes); (*ii*) Pharmacological treatment (e.g. paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs], topical treatments); (*iii*) Intra-articular intervention (injections, lavage); (*iv*) Surgical intervention (e.g. arthroplasty) (17).

Figure 2 presents a "stairway to surgery" approach to the management of knee OA, inspired by Dieppe & Lohmander as well as Jüni *et al* who used pyramidal presentations (13;18). However, it may be more relevant to look at the disease development in terms of a staircase, since most patients would most certainly recognise when they reach a new step. The intention is to highlight the need to stop (or slow down) the evidently expected steps towards surgery, especially among obese individuals with knee OA (19). In this interpretation of a pyramidal approach to therapy, the lower layer applies for all individuals in order to improve public health (20). The staircase interpretation builds on the fact that all knee OA patients should be given general advice about the disease (including lifestyle alterations the need of keeping fit and active and to lose weight if they are overweight). All patients ought to be empowered to take control of their condition themselves through self-help measures with proven effectiveness, such as use of simple analgesics (21) and topical agents (22), as well as some nutraceuticals (23).

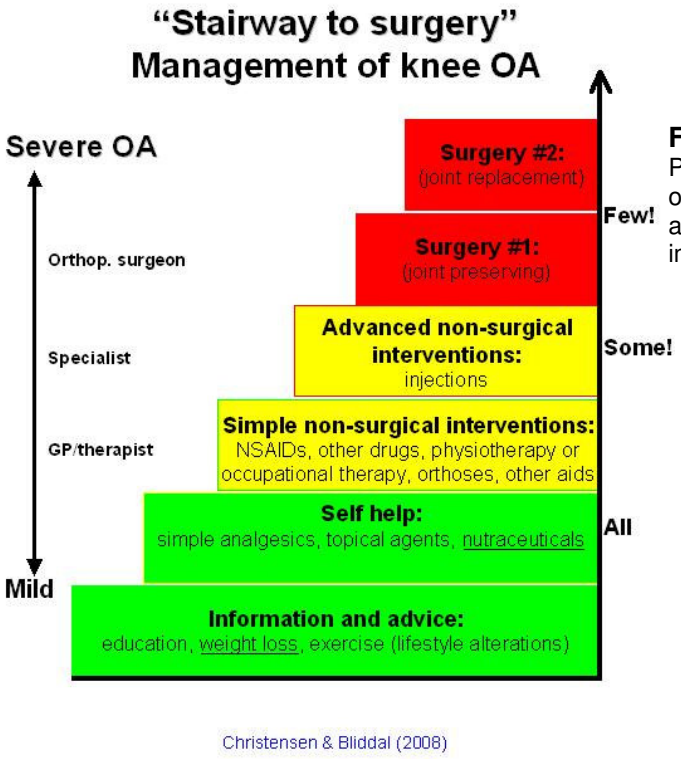

Figure 2:
Principles of management and consequences of osteoarthritis. Suggested sequential, stepwise approach to disease management; keeping up with impairment. (GP: general practitioner)

As illustrated in Figure 2, many patients try at least one nutraceutical as a positive attempt to improve their condition (24). Since OA treatment is limited by the inability of prescribed medications to alter disease outcome, taking specific food substances like nutraceuticals is hoped to affect the structural changes, which occur within a degenerating joint. The role of nutraceuticals in OA management, need to be defined by an evidence-based approach if one wishes to support their use. Nutraceuticals are functional ingredients sold as powders, pills, and other medicinal forms not generally associated with food (23), and as stated in the ***BOX: Nutraceuticals,*** the term has no regulatory definition and is not recognised by the U.S. Food and Drug Administration (FDA); FDA does though use the term 'dietary supplements' for these (25). According to the American rheumatologists Roy D. Altman and Marc C. Hochberg, all dietary components on the US market for symptomatic therapy of OA are explicitly launched as a supplement to improve 'joint health'. At present, FDA does not allow any explicit claims on nutraceuticals for OA therapy (personal communication, R.D. Altman & M.C. Hochberg, December 2007).

If the suggested measures applied at the level '*All*' fail (13), it is necessary to consider interventions requiring medical supervision such as non-steroidal anti-inflammatory drugs (26), physiotherapy (including supervised aquatic exercise (27)), and the use of aids and appliances. Towards the top of the OA staircase, for those where other measures have failed, more invasive interventions are necessary. Here, for those with severe OA, joint replacement is very effective (3;13).

BOX: Nutraceuticals

There is no consensus on the definition of nutraceuticals and functional foods: in a policy paper in 1999, Zeisel distinguished whole foods from the natural bioactive chemical compounds derived from them and available in a non-food matrix by using the term 'functional foods' to describe the former and nutraceuticals to describe the latter (28). According to this newer definition, nutraceuticals are functional ingredients sold as powders, pills, and other medicinal forms not generally associated with food (23).

Osteoarthritis and obesity (29)

The presence of OA in a high percentage of obese individuals has been known by epidemiologists for decades (30). Epidemiological data suggest that obesity is of great importance for the development of knee OA. There is a definite association between degree of weight bearing and development of OA in both knee (31) and hip joints (6). In fact, obesity is presumably the single most important risk factor for development of severe OA of the knee and more important than other potential damaging factors, including heredity (32). Obesity will increase the load on the knee, and when varus mal-alignment develops as a secondary condition to OA, as seen in about 50% of the patients, the resulting effect on the joint could well be responsible for the degeneration of the cartilage, measured by grade of severity in a cross-sectional material of OA patients (33). Furthermore, there is evidence pointing towards that the weight effect causing deterioration of OA over time is dependent on mal-alignment (34). One potentially confounding factor connected with the condition is the coexisting quadriceps weakness in obese OA patients (35), which may alone induce a higher impact on the cartilage during gait (36).

OA may be triggered by several other causes than biomechanical ones, and it has been suggested that there may be a yet unclarified genetic origin (37). Obesity is also given as a cofactor for development of OA in non-weight-bearing joints as, e.g. wrists and fingers (38;39). Hyper-insulinemia is, on the other hand, thought to play a role in the pathogenesis of OA based on the observation that OA patients suffering from obesity have increased plasma levels of insulin when compared to obese subjects without radiographic joint changes (40). Cytokines play an important

role in both obesity and OA: The cartilage in OA is susceptible to accelerated degeneration under the influence of pro-inflammatory cytokines (41), and in obesity, cytokines may play an important role as well (42). The influence of cytokines is reversible, which makes intervention all the more interesting (43;44). It is thus quite possible that the link between obesity and OA is of multi-factorial origin and not just a matter of excessive weight (45). In most obese patients, obesity is associated with a low-grade inflammation of white adipose tissue resulting from chronic activation of the innate immune system. This may subsequently lead to insulin resistance, impaired glucose tolerance and even diabetes. The name of adipokine is nowadays generally given to any protein that is synthesized and secreted by adipocytes (46). There is strong evidence that, for a given condition of obesity, there is a large heterogeneity in the metabolic and cardiovascular risk which is mainly linked to the location of excessive adipose tissue (47). The role of fat cells in metabolic dysfunctions has long been considered, but fat cells potential role in an inflammatory process is a new concept. Several findings have converged to indicate that adipocytes share certain properties with immune cells such as complement activation (48) and pro-inflammatory cytokine production (49).

For some time, obesity may be of limited importance for the functional status of the well-trained individual (50). With increasing age, however, the situation may not be stable. Any event may trigger deterioration of a fragile situation when an elderly obese or overweight person is exercising at maximum capacity (51). The cardinal symptom in OA is pain, which causes compensatory gait changes (52), and impact (53;54) and joint loadings at heel strike during walking are suspected as a co-factor in the development of knee OA (54). As a consequence, obesity may participate in the creation of a vicious circle of diminishing exercise, decreasing muscle strength, and increasing joint troubles in the elderly subject with both obesity and knee OA. The average body mass index (BMI) of the population is on the increase (55) and this causes severe problems to the general status of health (56;57). Accordingly, obesity must be taken seriously in any discussion of health, including that of the joints (29).

OBESITY

Prevalence

Obesity, defined as having a BMI of 30 kg/m^2 or more, is a chronic, progressive, relapsing disease. The prevalence of obesity is increasing exponentially, and obesity has reached epidemic proportions

(58). WHO describes obesity as one of the most blatantly visible, yet most neglected, public-health problems that threatens to overwhelm both developed and third world countries (58). It is only during the past 10 years that the problems related to overweight and obesity have achieved global recognition. This is in contrast to being underweight, mal-nurtured, or suffering from infectious diseases, which all have been dominating health issues at any time (59). Epidemiological data suggest that the risk of diabetes, hypertension, and dyslipidaemia increases from a BMI of about 21.0 kg/m^2 (58), thereby reducing life expectancy and greatly increasing the health and societal economic burden. Excess bodyweight has been estimated to be the sixth most important risk factor contributing to the overall burden of disease worldwide (60). There has been a pronounced, distinctive increase in the prevalence of obesity within almost all age groups of the Danish population during the last 25–30 years. There are several indications that the development of obesity amongst the Danish adult population resembles the development in several European countries, and recent studies support the notion of a continued increase in obesity prevalence (61). Bendixen *et al* studied self-reported weight and height of 10,094 men and 9,897 women in the 16 to 98 years age range, collected in a series of seven independent cross-sectional surveys (62). The prevalence of obesity and the risk of being obese have increased substantially between 1987 and 2001. In women, the prevalence of obesity has more than doubled between 1987 (5.4%) and 2001 (12.5%). In men, the prevalence of obesity increased from 5.6% in 1987 to 11.8% in 2001 (62). In men, the prevalence of overweight increased from 34% to 40% between 1987 and 2001, and this development was associated with a significantly increased risk of being obese (OR= 1.3). In women, the risk of being overweight increased significantly during the last years, and in 2001, 27% of the adult Danish women were overweight, which was associated with an overweight risk which had doubled from 1987 to 2001 (OR= 2.0) (62).

Co-morbidities

Obesity is the primary aetiological factor in a number of disease processes. A BMI greater than 30 kg/m^2 is associated with an increase in all-cause mortality (58). It is not just the amount of fat in the body, but also its distribution, that determines the risks of diseases associated with obesity. Abdominal or visceral fat (android obesity) is the type particularly associated with impaired glucose tolerance or type 2 diabetes, hypertension and dyslipidaemia, which contribute markedly to the risk of cardiovascular disease (CVD) and the health costs of obesity (63). Impaired glucose tolerance and diabetes are associated with higher plasma glucose and glycosylated haemoglobin (a long-term measure of plasma glucose control, HbA1c) (64). High levels of total cholesterol, low-density

lipoprotein (LDL) cholesterol and triglycerides increase a risk of CVD, as do higher levels of systolic and diastolic blood pressure. Conversely, low levels of high-density lipoprotein (HDL) cholesterol increase the risk of CVD, such that it may be beneficial to increase the levels of HDL (65). In general, the more obese a subject is the greater are the associated risk factors (66). Obesity-associated diseases may be classified into five major areas (58):

- chronic disease (including musculoskeletal diseases)(1)
- CVD/stroke
- cancer
- metabolic/endocrine disease
- psycho-social disease

Perhaps the most dominant obesity-related *medical* comorbidity, and the one which is likely to cause the greatest direct health-care cost, is type 2 diabetes mellitus. Around 70% of type 2 diabetes sufferers appear to have a BMI > 25 kg/m^2 (58). With increasing weight, the risk of developing type 2 diabetes increases exponentially (20;67). Obesity is a triggering factor in abnormal glucose metabolism, resulting in an insulin-resistant state. This may also be associated to abnormalities in lipid metabolism (64). Resources are primarily allocated to the treatment of the associated co-morbidities with major costs to society (59;68). As stated by Fontaine *et al,* obesity is a major public health problem that appears to lessen life expectancy markedly, especially amongst individuals in younger age groups. Estimates of years of life lost due to obesity strongly support the public health recommendation to adults: to avoid obesity (69).

Weight loss strategies

With the increasing prevalence of obesity, it is essential to assess and develop suitable treatment strategies, which will result in long-term weight reduction and maintenance of this weight loss. Obesity needs to be managed like any other chronic disease: with empathy and a non-judgmental professional attitude. Helping subjects to manage their weight is difficult and can be discouraging and time-consuming for health professionals. High recurrence rates, apparent lack of effectiveness, and lack of training and resources, are major obstacles. However, increasing evidence exists for the effective management of obesity. Also, resources for health professionals are now available. Treatment includes all aspects of dieting (70) and lifestyle alteration (20) with or without pharmacotherapy (71;72), and in some cases surgery (73;74). In almost every overweight and obese patient, the diet must be adjusted to reduce energy intake. Dietary therapy consists of instructing patients on how to modify their dietary intake to achieve a decrease in energy intake while

maintaining a nutritionally adequate diet (70). Due to their enlarged body size, obese patients have higher energy requirements than normal-weight subjects at any given level of physical activity (75). Reducing the obese patient's total energy intake compared to that of a normal-weight individual will inevitably cause weight loss, consisting of about 75% fat and 25% lean tissue, until weight normalization occurs at a new energy equilibrium (76). Consistent evidence shows that a long term, low-fat diet produces long term weight loss and beneficial changes in lipids, blood glucose, glycaemic control, and blood pressure. Diets with a deficit of 500–1000 kcal (i.e. 2090-4180 kJ) per day will produce a weight loss of between 300 and 1000 g per week, depending on the patient's weight. Total energy expenditure declines and normalizes along with weight loss, and total energy intake should therefore gradually be further reduced to maintain the energy deficit (70).

Typically, a diet would have a deficit of 500-600 kcal/day below the current requirement for energy balance, leading to a weight reduction of 0.5 kg a week. Very low energy diets (VLED) may produce better initial weight loss, which might improve motivation, but long-term weight loss (i.e., maintenance) achieved in this way is rarely any greater than the loss achieved with low fat diets (70). Weight loss is difficult to achieve, and maintaining the weight loss is an even greater challenge. The greater the initial weight loss, the better is the subsequent outcome. Such a predictor tells us that there is a consistent weight loss pattern from the beginning of the treatment. Initial weight loss may also reflect a better compliance with the treatment (77). It has been noted that the findings on initial weight loss challenge the clinical opinion that weight loss achieved at a slow rate would be better (78). In a Danish trial published in the British Medical Journal, Toubro and Astrup randomised obese subjects to either rapid or slow initial weight loss with a completion of the study with patients re-randomised to one year weight maintenance programme of *ad libitum* diet or fixed energy intake diet (79). At one year follow up, the patients allocated to *ad libitum*, low-fat, high carbohydrate diet showed superior results to fixed energy intake, maintaining weight after a major weight loss. The rate of the initial weight loss did not influence long-term outcome (79).

Diet and exercise play a central role in preventing obesity and are the first line treatment for the condition (20). Despite the availability of evaluated and approved obesity drugs - and even though some patients will have failed to lose weight after non-drug treatment, the medical profession have been reluctant to prescribe drugs (71). The reasons for this may include experience of adverse events with amphetamine and amphetamine-like drugs, and the serious complications when

combining phentermine and fenfluramine (80). Many patients also need drugs to help them lose weight, or to maintain the loss, whatever way this loss was achieved (80). At present, three drugs are available in the EU for long-term use: Orlistat, Sibutramine, and Rimonabant (71;80).

- *Orlistat* is an intestinal lipase inhibitor which is taken three times daily with meals. It generates malabsorption of 30% of dietary fat. It leads to 5-10% weight loss in 50-60% of patients, and in clinical trials the loss (and related clinical benefit) is largely maintained up to at least four years. According to the review by Rucker *et al* (2007) orlistat reduced weight by 2.9 kg (95% confidence interval 2.5 kg to 3.2 kg; 15 studies) or 2.9% (2.5% to 3.4%; 13 studies) more than placebo and increased the absolute percentage of participants achieving 5% and 10% weight loss thresholds by 21% (54% *v* 33%; 18% to 24%; 14 studies) and 12% (26% *v* 14%; 9% to 14%; 13 studies), respectively (71).
- *Sibutramine* inhibits the reuptake of noradrenaline and serotonin, promoting and prolonging satiety. It is taken once daily. Sibutramine produces 5-10% weight loss in 60-70% of patients, and in clinical trials the weight loss is well maintained for at least two years. If weight loss is less than 2 kg at four weeks, the dose may be increased from 10 mg to 15 mg. According to the review by Rucker *et al* (2007) patients receiving sibutramine lost 4.2 kg (3.6 kg to 4.7 kg; eight studies) or 4.3% (3.7% to 5.0%; 10 studies) more than those taking placebo. In addition, sibutramine treatment increased the absolute percentage of 5% and 10% responders by 32% (55% *v* 27%; 27% to 37%; seven studies) and 18% (28% *v* 10%; 11% to 25%; seven studies), respectively (71).
- *Rimonabant* is the first cannabinoid-1 receptor antagonist to be licensed for obesity treatment. Stimulation of cannabinoid-1 receptors in the brain promotes eating, and in peripheral tissues it affects cardiovascular risk factors such as low concentration of high-density lipoprotein cholesterol, insulin resistance, and inflammation. Blockade with rimonabant produces weight loss and weight-independent improvements of some cardiovascular risk factors. Rimonabant produces 5-10% weight loss in 60-70% of subjects, maintained for up to two years in clinical trials. According to the review by Rucker *et al* (2007) Patients receiving rimonabant lost 4.7 kg (4.1 kg to 5.3 kg; four studies) more than those taking placebo. The average weight loss was 3.9 kg (3.2 kg to 4.6 kg) in the rimonabant group in obesity-diabetes trials (71). Rimonabant treatment also significantly increased the placebo subtracted absolute percentage of 5% and 10% responders by 33% (51% *v* 18%; 29% to 37%) and 19% (26% *v* 7%; 15% to 23%), respectively (71).

Two recent reports have uncovered a worrying link between the antiobesity drug rimonabant and mental health problems, including suicide (81). The first, a meta-analysis by Christensen *et al* of four key (phase III) trials (72), found that obese subjects who used the drug were two and half times more likely than placebo controls to stop their treatment due to depression or depressive symptoms (74/2503 [3.0%] *v* 22/1602 [1.4%]; odds ratio 2.5, 95% CI: 1.2 to 5.1), and it was three times more likely that they would stop treatment due to anxiety (26/2503 [1.0%] *v*. 5/1602 [0.3%]; 3.0, 1.1 to 8.4). Keeping in mind that all the included weight loss trials excluded patients with existing mental illness. A second report, prepared for the US Food and Drug Administration, found that 26% of patients who was treated with rimonabant had some kind of adverse psychiatric event, compared to14% of those who was given placebo (relative risk 1.9, 1.5 to 2.3) (81). In an extended analysis including smoking cessation trials, the odds ratio for suicide in people taking rimonabant was 1.9 (1.1 to 3.1). These results raise serious concerns about the safety of rimonabant, particularly for obese people who are prone to depression (81). Rimonabant is already available in Argentina, Austria, Denmark, Finland, Germany, Ireland, Norway, Sweden, Greece, and the UK. In the US, the FDA is now asking for more safety data before making a licensing decision.

EVIDENCE-BASED METHODOLOGY

Evidence-based medicine

The successful introduction of clinical guidelines is dependent on many factors, including the clinical context and the methods of developing, disseminating, and implementing those guidelines. Different methods will be appropriate in different contexts. Only if appropriate strategies are selected at each stage will clinical guidelines achieve the full potential (82). "*Most doctors have a very narrow perspective, limiting themselves to their own experience and that of a relatively few colleagues with whom they exchange views. This sometimes leads them to make erroneous conclusions. In their narrowness they fail to search for evidence, which might cause them to reach a different conclusion or allow them to come to a more balanced decision*" (83).

Evidence-based medicine is the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions. For decades, health professionals have been aware of the gaps between research evidence and clinical practice, and the consequences

in terms of expensive, ineffective, or even harmful decision making (84). The term "Evidence-based Medicine" was coined at McMaster Medical School in Canada in the 1980s to label the clinical learning strategy the school had developed for over a decade (84). The philosophical origins of evidence-based medicine extend back to the mid-19th century Paris and earlier, and evidence-based medicine remains a hot topic for clinicians, public health practitioners, purchasers, planners, and the public (85). Evidence-based medicine may be practised in any situation where there is doubt about an aspect of clinical diagnosis, prognosis, or management (84). Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence when making decisions about the care of individual patients. Practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research (85). Rosenberg and Donald presented four essential steps in evidence-based medicine: (I) Formulate a clear clinical question from a patient's problem; (II) Search the literature for relevant clinical articles; (III) Evaluate (critically appraise) the evidence for its validity and usefulness; (IV) Implement useful findings in clinical practice (84). Evidence-based medicine is not restricted to randomised trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions. According to Eccles, categories of evidence were adapted from the classification of the United States Agency for Health Care Policy and Research, i.e. clinical questions answered based on the best evidence available (86). If, for example, a question on the effect of an intervention could be answered by category I evidence, then studies of weaker design (controlled studies without randomisation) were not reviewed (86). This categorisation of (best) evidence is presented in a hierarchical form in **Table 2A**, representing the most appropriate way to answer questions of causal relations.

Table 2A: Categories of evidence

Ia	Evidence from meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
IIa	Evidence from at least one controlled study without randomisation
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from descriptive studies, such as comparative studies, correlation studies and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Table 2B: Strength of recommendation

A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

Eccles *et al*. ***BMJ*** 1998;316:1232-1235

Recommendations were derived based on informal consensus methods (**Table 2B**) and reflect the certainty with which the effectiveness and cost effectiveness of a medical intervention are recommended. Recommendations are based upon consideration of the following: strength of evidence, applicability of the evidence to the population of interest, economic considerations, values of the guideline developers and society, and guideline developers' awareness of practical issues (86). While the process of interpreting evidence inevitably involves value judgments, Eccles *et al* clarified the basis of these judgments as far as possible by making this process explicit, as presented in Table 2.

Evidence-based rheumatology (87)

Evidence-based rheumatology is the application of the most valid scientific information to the care of patients with rheumatic diseases. Physicians who treat patients with musculoskeletal diseases must provide their patients with the most effective and safest therapy. To meet this high standard, individual clinicians must have access to, and be able to evaluate, scientific evidence. Although many practitioners argue that this has always been the standard of care in clinical medicine, a great deal of evidence exists to the contrary (88). In rheumatology, the appreciation and application of the advances in psychometrics and clinimetrics have not been adopted quickly. Patient-reported outcomes (PROs) have always had face validity but had to await the demonstration of adequate psychometric and clinimetric performances. This is a major stimulus for the involvement of the OMERACT (*Outcome Measures in Rheumatology*) meetings to date, since these are directly associated with evidence-based rheumatology.

Relevant outcomes are necessary but not sufficient. The choice of outcomes is but one of the elements of study design that is needed to arrive at the best estimates of benefits and harms for therapeutic interventions. There is now a general acceptance of that randomised trials, when feasible, will provide the most rigorous estimates (and where these are available, this text will restrict itself to them). Although RCTs are the most valuable source of data for evaluating healthcare interventions, other kinds of evidence must sometimes be used. In some instances, most obvious in studies of drug toxicity with rare or delayed effects, it is neither possible nor ethical to perform RCTs. Here, data from methodologically rigorous, observational studies are extremely valuable (89).

The systematic review of RCTs typically considered the essential first-step in any meta-analysis (90). Compared to a narrative literature review, the systematic review employs "*scientific strategies that limit bias in the assembly, critical appraisal and synthesis of all relevant studies on a specific topic"* (91). The aim of the Cochrane Collaboration is to help physicians, patients, and policymakers make well-informed decisions on healthcare treatments by preparing, maintaining, and disseminating high-quality systematic reviews (http://www.cochrane.org/). The *Cochrane Musculoskeletal Group* (CMSG). One of 50 international groups in the Cochrane Collaboration (http://www.cochranemsk.org/), synthesizes the results of studies to determine the effectiveness and safety of interventions for the prevention, treatment, and management of musculoskeletal diseases including various forms of arthritis (92). The Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane-handbook.org/) describes in detail the process of creating Cochrane systematic reviews. A crucial step in the preparation of *any* systematic review is to develop the method by which all relevant trials concerning a specific topic will be identified. First, however, the research question needs to be clearly formulated using the "PICO" framework, i.e., a clinical or research question that takes into account the Patient/Population, Intervention, Comparison, and Outcomes (92).

The extent to which a review can draw conclusions about the effects of an intervention applied in rheumatology depends on whether the data and results from the included studies are valid. In particular, a meta-analysis of invalid studies may produce a misleading result, yielding a narrow confidence interval around the wrong intervention effect estimate. The evaluation of the internal validity of the included studies is therefore an essential component of a systematic review, and should influence the analysis, interpretation and conclusions of the review (93). Empirical studies show that inadequate quality of trials may distort the results from systematic reviews and meta-analyses. Jüni *et al* emphasised that the generation and concealment of the allocation sequence, blinding, and handling of patient attrition in the analysis should always be assessed (93). The robustness of the findings of a meta-analysis to different assumptions should always be examined in a thorough sensitivity analysis (94). However, stratified analyses and meta-regression models are useful when exploring associations between treatment effects and study characteristics (95).

In statistical literature the idea of evaluating *bias* is recognised especially within statistical inference theory when discussing bias in 'point estimation'; i.e., for an unknown parameter of interest (e.g., μ) a single value is estimated from the data (e.g., m_i) consisting of n_i observations and used as an estimate of that parameter (e.g., a mean value, m). In statistical terminology, an *unbiased* estimator for a parameter is defined as one that would on average result in the '*true'* value (i.e., potentially discovered if the trial was replicated *many* times). Intuitively this means that the parameter estimate is *unbiased* if the distribution of estimates (i.e., results from many trials, k) is centred at the '*true*' value, and there is no persistent tendency to under- or overestimate the '*true*' parameter (96). Bias ($B = m - \mu$) would be defined as the average error-term from gathering multiple estimates following an infinite number of trials ($k = \infty$). According to this, an estimate would be considered *unbiased* if the expected error from estimation equals zero (i.e., if $B \rightarrow 0$ when $k \rightarrow \infty$), and vice versa for *bias* (if $B \rightarrow b \neq 0$ when $k \rightarrow \infty$).

According to the *Cochrane Handbook for Systematic Reviews of Interventions* there are some general guidelines on how to define 'bias' when performing systematic reviews (see **BOX: Bias**).

BOX: Bias

A bias is a systematic error, or deviation from the truth, in results or inferences. Biases can operate in either direction: different biases can lead to underestimation or overestimation of the true intervention effect. Biases can vary in magnitude: some are small (and trivial compared with the observed effect) and some are substantial (so that an apparent finding may be entirely due to bias). Even a particular source of bias may vary in direction: bias due to a particular design flaw (e.g., lack of allocation concealment) may lead to underestimation of an effect in one study but overestimation in another study. It is usually impossible to know to what extent biases have affected the results of a particular study, although there is good empirical evidence that particular flaws in the design, conduct and analysis of randomised clinical trials lead to bias. Because the results of a study may in fact be unbiased despite a methodological flaw, it is more appropriate to consider risk of bias.

http://www.cochrane-handbook.org/

Strength of quality of evidence in rheumatology (88)

In an effort to make it easier for the end user to understand the strength of the quality of the evidence included in a review, CMSG recommends that an overall grade of the evidence for each major outcome must be provided in each review. This simplified grading system focuses on a few validated criteria to decide which studies warrant the highest levels of Gold and Platinum, namely adequate sample size, completeness of follow up, blinding of outcome assessors and patients, and concealment of allocation. There are 4 categories to rank the evidence from research studies: *Platinum*, *Gold*, *Silver*, and *Bronze* (88):

Platinum level

The Platinum ranking is given to evidence that meets the following criteria, as reported: there must be at least 2 individual randomised controlled trials included, each satisfying the following:

• Sample sizes of at least 50 per group. If they do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome

• Blinding of patients and assessors for outcomes

• Handling of withdrawals > 80% follow-up [imputations based on methods such as last observation carried forward (LOCF) acceptable]

• Concealment of treatment allocation

Gold level

The Gold ranking is given to evidence if at least one randomised controlled trial meets all of the following criteria:

• Sample sizes of at least 50 per group. If they do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome

• Blinding of patients and assessors for outcomes

• Handling of withdrawals > 80% follow-up [imputations based on methods such as LOCF acceptable]

• Concealment of treatment allocation

Silver level

The Silver ranking is given to evidence from a randomised trial that does not meet the above criteria. Silver ranking would also include evidence from at least one study of nonrandomised cohorts who did and did not receive the therapy or evidence from at least one case-control study. A randomised trial with a "head-to-head" comparison of agents is considered Silver level ranking, unless a reference is provided comparing of one of the agents to placebo, showing at least a 20% relative difference.

Bronze level

The Bronze ranking is given to evidence if at least one case series without controls (including simple before/after studies in which the patient acts as their own control) or is derived from expert

opinion based on clinical experience without reference to any of the foregoing (for example, argument from physiology, bench research, or first principles).

Monitoring osteoarthritis progression and therapy

Monitoring progression of OA and effects of therapy during clinical trials require valid and reliable outcome measurements. Effective outcome measures are critical to many aspects of osteoarthritis research and in particular critical to clinical trials studying new types of treatment (97). Outcome measures in OA research include patient-relevant measures, structural measures and process biomarkers in the form of molecules or molecular fragments: In 1996, during the OMERACT 3 conference, using a combination of discussion and polling procedures, a consensus was reached by at least 90% of participants (98). The result was that the following 4 domains should be evaluated in future phase III trials of knee, hip, and hand OA: pain, physical function, patient global assessment, and, for studies of one year or longer, joint imaging (using standardized methods for taking and rating radiographs, or any imaging technique demonstrated to be superior to radiographs) (98). Within each of the three core domains related to symptom severity, several measurement instruments may be considered (99). Pain is often measured with a simple visual analogue scale (VAS) (100) and functional impairment/physical function with the Western Ontario McMasters Universities Osteoarthritis (WOMAC) Index (101). In parallel to the WOMAC questionnaire, the Knee injury and Osteoarthritis Outcome Score (KOOS) consists of 5 subscales; (i) Pain, (ii) other Symptoms, (iii) Function in daily living (ADL), (iv) Function in sport and recreation (Sport/Rec) and (v) knee related Quality of life QOL (102); standardized answer options are given (5 Likert boxes), and each question gets a score from nought to four. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. Global assessment may be evaluated with a Likert scale or a VAS, which is easier to analyze from a statistical point of view. Other possible instruments include the Lequesne Functional Severity Index (103) and the Arthritis Impact Measurement Scales (AIMS) (104). Imaging techniques may consist of radiography, magnetic resonance imaging (MRI), or other similar imaging techniques (99). Any imaging technique employed requires standardized methods for both taking and scoring images (98;99).

According to the International Classification of Functioning, Disability and Health (ICF) definitions, the items assessed should be applicable for one or more ICF construct,

i.e. Impairment (I), Activity Limitation (A), and Participation Restriction (P) (105). To date, however, making use of the available instruments may either mask true treatment effects or make an effect difficult to attribute if the chosen outcome measure does not describe the chosen effect (106).

METHODS

Systematic Literature Search

Performing a literature search is a vital step in the evidence-based process. The process of searching for information is not simply a matter of plugging in a few keywords into one's favourite search engine. Very unfortunate outcomes may result from a search that does not locate all the appropriate literature – with, for example, a biased summary measure being highly likely. As mentioned previously (being part of the PICO format), the first step in the evidence-based process is to identify a clinical question or questions arising from a clinical scenario. The literature search is the second step *per se*.

In the present thesis, which focuses on the importance of dietary factors in knee osteoarthritis, the following PICO filter was part of the search strategy, filtering the literature search according to Medical Subject Heading (MeSH) terms:

- **P**atients (i.e. Osteoarthritis, Knee [MeSH])
- **I**ntervention (i.e. Dietary Supplements [MeSH]/Body Weight Changes [MeSH])
- **C**omparing the experimental therapy with a placebo/control
- **O**utcomes of interest will be the so-called (OMERACT 3) core set variables

Assuming that most of the available literature assesses efficacy using the OMERACT 3 recommended outcomes (i.e. Pain, Disability, and Global assessment) (98;99).

Meta-Analysis

In order to do a general search for interventions applied and assessed systematically in knee OA, the search filter presented by Hunt *et al* (107) would be a relevant first step. Hunt *et al* presented a filter designed to locate meta-analyses and systematic reviews:

1. meta-analysis.pt,sh
2. (meta-anal: OR metaanal:).tw
3. (quantitative: review: OR quantitative: overview).tw

4. (methodologic: review: OR methodologic: overview:).tw
5. (systematic: review: OR systematic: overview).tw
6. review.pt. AND medline.tw

Using the PubMed search syntax:
[pt] denotes a Publication Type term; [tiab] denotes a word in the title or abstract; [sh] denotes a subheading; and [tw] denotes a text word.

Resulting in the following search in PUBMED (107):
("meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[Text Word]) OR ((quantitative[All Fields] AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[Text Word])) AND (quantitative[All Fields] AND overview[All Fields])) OR ((methodologic[All Fields] AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[Text Word])) AND (methodologic[All Fields] AND overview[All Fields])) OR ((((("classification"[TIAB] NOT Medline[SB]) OR "classification"[MeSH Terms] OR systematic[Text Word]) AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[Text Word])) AND ((("classification"[TIAB] NOT Medline[SB]) OR "classification"[MeSH Terms] OR systematic[Text Word]) AND overview[All Fields])).

Randomised Controlled Trials
In order to search for individual relevant studies, the *Cochrane Highly Sensitive Search Strategy for identifying randomised trials* in MEDLINE (PubMed format) applied:

1. randomized controlled trial [pt]
2. controlled clinical trial [pt]
3. randomized [tiab]
4. placebo [tiab]
5. drug therapy [sh]
6. randomly [tiab]
7. trial [tiab]
8. groups [tiab]
9. = #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10. humans [mh]

11. #9 and #10

Using the PubMed search syntax:
[pt] denotes a Publication Type term; [tiab] denotes a word in the title or abstract; [sh] denotes a subheading; [mh] denotes a Medical Subject Heading (MeSH) term ('exploded');
[mesh: noexp] denotes a Medical Subject Heading (MeSH) term (not 'exploded'); [ti] denotes a word in the title.

Patients

In order to search for relevant patients/participants, the search filter presented by Reichenbach *et al* (108) applied; a filter designed to locate studies including OA patients:

1. osteoarthriti$.ti,ab,sh.
2. osteoarthro$.ti,ab,sh.
3. gonarthriti$.ti,ab,sh.
4. gonarthro$.ti,ab,sh.
5. coxarthriti$.ti,ab,sh.
6. coxarthro$.ti,ab,sh.
7. arthros$.ti,ab.
8. arthrot$.ti,ab.
9. ((knee$ or hip$ or hand$ or finger$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ti,ab.
10. ((knee$ or hip$ or joint$) adj3 stiff$).ti,ab.

Resulting in the following search in PUBMED:
(osteoarthritides OR arthritis, degenerative OR arthritides, degenerative OR degenerative arthritides OR degenerative arthritis OR osteoarthrosis OR osteoarthroses OR osteoarthrosis deformans OR knee osteoarthritides OR knee osteoarthritis OR osteoarthritides, knee OR hip osteoarthritis OR hip osteoarthritis OR osteoarthritides, hip OR coxarthrosis OR coxarthroses).

Interventions

The dietary trials discussed in the systematic review by Ameye and Chee were carefully scrutinised as they expanded their search strategy (23). As stated by Ameye and Chee: numerous valid trials that were already known to them were not selected by such searches. Hence, to be as exhaustive as possible, they changed their strategy and, instead of focusing on nutrition, devised a systematic

search aiming at selecting all clinical trials in OA (23). This search of clinical trials in OA was fine-tuned for each database: (*i*) PUBMED was searched by using the following strategy: random* AND (double-blind method [mh] OR (trial? OR stud??? OR placebo)) AND osteoarthritis [mh]; (*ii*) EMBASE was searched with the following keywords: (double near blind OR trial? OR stud??? OR placebo) AND osteoarthritis. BIOSIS was searched with the following keywords: random* AND (double near blind OR trial? OR stud??? OR placebo) AND osteoarthritis.

Statistical Analysis

Statistical inference

Inferential statistics or statistical induction comprises the use of statistics to make inferences concerning some unknown aspect of a population. Inference is concerned about a population from a random sample drawn from the population in question or, more generally, about a random process from its observed behavior during a finite period of time. There are three main types of statistical inference, namely (*i*) point estimation, (*ii*) interval estimation and (*iii*) hypothesis testing (96).
(*i*) In point estimation, a single value is computed from the data and used as an estimate of that parameter ($E[Y]$) for each unknown parameter of interest (e.g. θ). (*ii*) Interval estimation provides a range of values which have a predetermined *high* probability (e.g. 95%) of including the true, but unknown, value of the parameter (e.g., 95% confidence interval for θ: $E[Y] \pm 1.96\times$Standard Error of the estimate (109)). (*iii*) Hypothesis testing tests specific hypotheses regarding the parameters of interest and assesses the plausibility of any specified hypothesis (typically the Null-Hypothesis: H_0) by testing whether the observed data support or refute that hypothesis (e.g., $H_0 : E[Y] = 0$ opposed to the Alternative Hypothesis $H_A : E[Y] \neq 0$ corresponding to a two-tailed statistical test (109)). As well as the different types of inference, there are also different underlying philosophies. The most widely used approach is the frequentist, classical or sampling theory approach (110): The theory makes the assumption that we can randomly take repeated samples of data under the same conditions as hold for our single observed sample from the same population (110;111).

The present PhD thesis is based on the classical (frequentist) sampling theory approach. Although, as will be discussed later, a meta-analysis handling patients within studies, estimating parameters using *priors*, constitutes a hierarchical model (96) which look a lot like Bayesian statistics (112). In a fully Bayesian analysis we would rely on external (subjective) evidence as our *prior* information, whereas a random-effects meta-analysis uses the observed data (i.e. prior studies available) to

estimate these final stage parameters and then proceeds as though the *prior* were known (112). As a consequence, random-effects meta-analyses might be considered an *empirical Bayes* procedure (113;114).

Meta-Analysis in Context

Applying large RCTs is the most reliable way to test whether a treatment causes benefit (or harm) in health (86); e.g., a new anti-obesity agent applied within a population of obese individuals. The most efficient type of field experiment (e.g. a clinical study) is that in which a replicated trial (e.g. a RCT) is laid down in the same year at a number of centres, or carried out at the same centre independently throughout a number of years as stated by WG Cochran in 1937 (115). When we are trying to make the best estimate of some quantity that is available from the research conducted to date (i.e. prior knowledge), the problem of combining results from different experiments is encountered (116). Structured multi-centre settings would be an elegant way to make clinical inference, although such research strategies might be prone to bias, as these are expensive and only possible if there is a willing sponsor at hand. Suppose that we instead wish to evaluate evidence and possibly quantify the clinical efficacy from many published, assumed mutually independent trials, we would carry out a systematic review and where appropriate apply meta-analysis (86;90).

Primary analysis is the original analysis of data in a research study, whereas secondary analysis is the re-analysis of data for the purpose of answering the original research question with better statistical techniques, or answering new questions with old data - i.e. meta-analysis (117). Meta-analysis has previously been defined as the statistical analysis of a collection of analytic results for the purpose of integrating the findings (118). Thus, combining the results from all available RCTs (evidence category 1b (86)), applying a systematic review and an appropriate meta-analysis strategy, represents a constructive alternative to more studies - strengthening the evidence (category 1a) about the treatment efficacy (86). A meta-analysis may be viewed as an extreme form of multi-centre study (119). By combining information across multiple studies, an integrated (meta-) analysis has more power to detect a treatment effect than an analysis based on only one study (120). There are numerous ways in which bias is introduced in reviews and meta-analyses of controlled clinical trials. If the methodological quality of the included trials is inadequate, the findings/conclusions of the reviews of this material may also be compromised. As stated by Thompson and Pocock: "*Meta-analysis is not an exact statistical science that provides definitive simple answers to complex clinical problems. It is more appropriately viewed as a valuable objective descriptive technique,*

which often furnishes clear qualitative conclusions about broad treatment policies, but whose quantitative results have to be interpreted cautiously" (94).

The role of meta-analyses in the regulatory process concerning foods, drugs, and devices has previously been discussed in Journal of the American Medical Association, in which the so-called "meta-experiment" was recommended (121). The industry ought to plan meta-experiments rather than *only* financing individual (large scale) RCTs. A pre-planned meta-analysis strategy would support evidence-based decision making. Meta-experiments should therefore be encouraged rather than simply performing *post hoc* meta-analyses (121). Considering the possible roles of meta-analysis in the approval process, Berlin and Colditz stated: "*We contend, however, that at least under some conditions, a meta-analysis could and should be used to provide independent substantiation of efficacy. In at least some situations, the meta-analysis, by substituting for an additional (not-yet-conducted) large trial, could accelerate the approval process*" (121).

Statistical Analysis: Individual Studies

The starting point of all meta-analyses of studies of effectiveness involves the identification of the data type for the outcome measurements. Broadly speaking, quantitative outcomes from any study can be classified as belonging to one of three data types: (*i*) binary, e.g., often indicating the presence or absence of the event of interest in each patient; (*ii*) continuous, where outcome is measured on a continuous scale, e.g. change in body weight and similar; or (*iii*) ordinal, where outcome is measured on an ordered categorical scale, e.g. a disease severity scale, where a patient is classified as belonging to one of several distinct categories.

In order to do a meta-analysis, we start by computing a summary statistic for each study considered eligible for inclusion in the meta-analysis. The ways in which the effect of a treatment can be measured depends on the nature of the data being collected. If a study reports mean values and SDs for two groups (e.g. change in pain status (99;100)), we may compute a mean difference (MD) or a standardised mean difference (SMD); whereas if a study reports counts (e.g. the number of responders to therapy (99;122)) for two groups, we may compute an Odds Ratio (OR) or a Risk Ratio (RR) (123). These summary statistics (i.e. effect measures) from the various studies then serve as the raw data in the meta-analysis. Every effect measure (MD, SMD, OR, or RR) should be accompanied by some index of precision. Precision may be reported via the standard error (*SE*), the variance, or by giving the confidence interval. These three parameters are related to each other.

Normand presented a thorough tutorial in *Statistics in Medicine*, demonstrating how to calculate these estimates and standard errors using study summary statistics for binary and continuous measurements (120). As presented below, a meta-analysis procedure is commonly referred to as an inverse-variance method. The weight given to each study is chosen to be the inverse of the variance of the effect estimate (i.e. one over the square of its standard error: $1/SE_i^2$). The basic data required for the analysis are therefore an estimate of the treatment effect (E_i) and its standard error (SE_i) from each study. As a consequence the statistical algorithms used in any meta-analysis can be expressed in terms of $E_i \pm SE_i$.

Statistical Analysis: Formulae for Combining Results across Studies

The simplest way to combine estimates is to average them. However, since different studies estimate the true effect size with varying degrees of precision, a weighted average is used. As mentioned previously, the weight (W) given to each study (i) in the meta-analysis is calculated by: $W_i = 1/SE_i^2$ (116). Based on this weighting, the combined weighted estimate (E) can easily be calculated, corresponding to a fixed-effects ($_F$) meta-analysis:

$$\boldsymbol{E_F = \Sigma(E_i \times W_i) / \Sigma W_i.}$$

With the corresponding fixed-effects model standard error (SE_F) being:

$$\boldsymbol{SE_F = (\Sigma W_i)^{-1/2}}$$

When performing a meta-analysis, although the overall aim may be to produce an overall pooled estimate of treatment effect, it is crucial to assess the variation between results of the primary studies and, if possible, to investigate why they differ (95). Clearly, it would be remarkable if all studies being meta-analysed produced exactly the same treatment effect estimate. Some variation in results is expected, simply due to chance. This is often called random variation.

Meta-Analysis: Test for Heterogeneity - Measuring Inconsistency

A formal statistical test of homogeneity (116), usually called a test for heterogeneity, is available. Such tests are sometimes used to decide which method - the fixed-effect or the random-effects - is more appropriate for a particular meta-analysis. An alternative approach is to consider the random effects method by default and assess the robustness of the findings using the fixed-effect method for sensitivity despite a failure in the assumption of homogeneity (124).

The usual test statistics for homogeneity is the Cochran *Q*-test, which can be used for any measure of treatment effect. The expression of the *Q*-test takes the form:

$$Q = \Sigma[(E_i - E_F)^2/SE_i^2]$$

and has an approximate χ^2 distribution, with k - 1 degrees of freedom under the null hypothesis of homogeneity (116). The extent of heterogeneity in a meta-analysis partly determines the difficulty in drawing overall conclusions. This extent may be measured by estimating a between-study variance, but interpretation is then specific to a particular treatment effect metric. Higgins and Thompson developed measures of the impact of heterogeneity on a meta-analysis from mathematical criteria which are independent of the number of studies and the treatment effect metric (125). They concluded that two measures - H and I^2 - are particularly useful summaries of the impact of heterogeneity. In a paper published in the British Medical Journal in 2003, Higgins *et al* showed that I^2 focuses attention on the effect of any heterogeneity of the meta-analysis, and an interpretation is intuitive: the percentage of total variation across studies due to heterogeneity (126). They concluded that I^2 is preferable to a test for heterogeneity in judging consistency of evidence (126). I^2 is readily calculated from basic results obtained from a typical meta-analysis:

$$I^2 = (Q - [k - 1])/Q \times 100\%$$

A naive categorisation of values for I^2 would not be appropriate in all circumstances, although Higgins *et al* tentatively assigned adjectives of low, moderate, and high to I^2 values of $\leq$25%, $\leq$50%, and $\leq$75% (126).

Random-Effects (empirical Bayes) Meta-Analysis

The fixed effect model discussed above starts with the assumption that the true effect is the same in all studies. However, this assumption may be implausible in many systematic reviews. When we decide to incorporate a group of studies in a meta-analysis, we assume that the studies have enough in common to justify a synthesis of the information. This is done despite the fact that there is generally no reason to assume that the studies are "identical" in the sense that the true effect size is exactly the same in all the studies (127). Rather than assuming that there is one true effect, we allow that there is a distribution of true effect sizes. The combined effect cannot therefore represent the one common effect but instead represents the mean of the population of true effects. An effect is classified as a random effect when you wish to make inferences on an entire population, and the

levels in your 'experiment' represent only a sample from that population. If all the effects in a model (except for the intercept) are considered random effects, then the model is called a *random-effects model*. Likewise a model with only fixed effects is called a *fixed-effects model*. The more common case, where some factors are fixed and others are random, is called a *mixed model* (128). The sequence of parameters and priors constitutes a hierarchical model. The hierarchy must stop at some point, with all remaining *prior* parameters assumed known (e.g. we handle the observed study variances as being 'true'). Allowing the observed data to play some role in determining the *prior* distribution produces the *empirical Bayes* (EB) approach. The EB approach uses the observed data to estimate the parameters and then proceeds as though the *prior* were known (112).
As stated by Raudenbush and Bryk: "*Empirical Bayes meta-analysis may be viewed as a special case of a two-stage hierarchical linear model*" (113). The first stage would be defining the within-study model, estimated separately for each publication, and handle these as being parameters varying randomly across studies. Thus it is logical to pose a second stage i.e. between-study model.

When SAS software is used for meta-analyses (72), I will refer to random-effects meta-analyses as using the restricted maximum likelihood (REML) method via a mixed model procedure (120;129). PROC MIXED fits a variety of mixed linear models to data and enables you to use these fitted models to make statistical inferences about the data (130). The default fitting method maximizes the restricted likelihood of the data under the assumption that the data are normally distributed and any missing data are missing at random. This general framework accommodates many common correlated-data methods, including variance component models and repeated measures analyses (131). The REML method (132), being the default setting in PROC MIXED, is a method for estimating variance components in a general linear model. Using the marginal distribution for E_i, the log-likelihood to be maximized allows us (iteratively) to estimate the between-study variance: τ^2 (120). From a computational point of view, PROC MIXED does the REML estimation via the following matrix structure (130):

$$\mathbf{E} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\boldsymbol{b} + \boldsymbol{e}$$

where E is the $(k \times 1)$ vector of summary statistics (i.e., effect sizes) from a number of k-related but independent studies, X $(k \times p)$ is the design matrix describing study characteristics (covariates) that influence fixed effects, β $(p \times 1)$ is the vector of fixed-effects parameters, Z $(k \times q)$ is another design matrix describing the covariates for the random effects, b $(q \times 1)$ is the vector of random

effects or the residuals on the between-study level (i.e., τ^2), and finally e ($k \times k$) is the matrix of residuals on the within-study level (i.e. SE_i^2).

As a note of caution, when review authors are concerned about the influence of small-study effects on the results of a meta-analysis in which there are *some* evidence of between-study heterogeneity ($\tau^2>0$ and $I^2>0\%$), they compare the fixed- and random-effects estimates of the intervention effect (133). If the estimates are similar, any small-study effects have little effect on the intervention effect estimate (94). If the random-effects estimate is more beneficial (i.e., incl. a careful consideration of the confidence intervals), review authors should consider whether it is reasonable to conclude that the intervention was more effective in the smaller studies (95;134).

Exploring Statistical Heterogeneity: Subgroup and Meta-Regression Analysis

It is important to consider to what extent the results of studies are consistent. If confidence intervals for the results of individual studies (generally depicted graphically using horizontal lines) have poor overlap, this generally indicates the presence of statistical heterogeneity. It assesses whether observed differences in results are compatible with chance alone. A number of options are available if statistical heterogeneity is identified among a group of studies ($I^2 >>0\%$) that would otherwise be considered suitable for a meta-analysis (94). It is clearly of interest to determine the causes of heterogeneity among results of studies (127). This process is problematic since there are often many characteristics that vary across studies. Heterogeneity may be explored by conducting subgroup analyses (i.e., stratifying the analysis according to a factor with well-defined levels) (93;135) or meta-regression analysis (136;137). Ideally, investigations of characteristics of studies that may be associated with heterogeneity should be pre-specified in the protocol of a review (124). Reliable conclusions may only be drawn from analyses that are truly pre-specified prior to inspection of the studies' results, and even these conclusions must be interpreted with caution (135;137). Explorations of heterogeneity that are devised after heterogeneity is identified may at best lead to the generation of hypotheses (95;135). Thompson and Sharp compared a number of methods which may be used to investigate whether a particular covariate, with an aggregate value defined for each study in the meta-analysis, will explain any heterogeneity (124). They concluded that methods, which allow for an additive component of residual heterogeneity should be used. In weighted regression, a REML-estimator is appropriate although a number of other estimators are also available (124). Furthermore, methods which use the original form of the data explicitly, for

example the binomial model for observed proportions rather than assuming normality of the log-odds ratios, are now computationally feasible (124). Although such methods are preferable in principle, they often do not change the results in practice (137).

RESULTS AND DISCUSSION

The CONSORT (Consolidated Standards of Reporting Trials) Statement, published in 1996 and revised in 2001, is a set of guidelines designed to improve the reporting of RCTs (138). Non-pharmacological treatment includes surgery, technical procedures, devices, rehabilitation, psychotherapy, behavioural interventions, and complementary and alternative medicine (incl. nutraceuticals). Non-pharmacological trials often test complex interventions involving several components. Such treatment is consequently difficult to describe, standardize, reproduce, and administer consistently to all patients. All of these variations could have an important impact on the estimate of the treatment effect; empirical evidence suggest that the use of the CONSORT guidelines is associated with improved quality of reporting in RCTs (139). It is of great importance that osteoarthritis trials using a dietary approach are performed in accordance with the CONSORT statement (140;141). This applies for weight loss (142) as well as for use of nutraceuticals (143;144). In analogy, health-care providers and other decision-makers now have, as part of their information resources, the meta-analysis, which enables a single combined estimate categorised as the highest degree of evidence: category 1a (see Table 2). These integrative systematic reviews may be helpful when making clinical decisions, and they may also serve as the foundation of the evidence-based practice guidelines, economic evaluations, and future research agendas. Like any other research enterprise, particularly one that is observational, the meta-analysis of evidence can be flawed as discussed. The QUOROM (Quality of Reporting of Meta-analyses) conference was convened to address standards for improving the quality of reporting of meta-analyses of RCTs. The resulting QUOROM statement was proposed in order to generate further thought about ways of improving quality of reports of meta-analyses of RCTs (90). The QUOROM statement describes items to include in a meta-analysis, based on empirical evidence whenever possible. This implies the need to include items that can systematically influence estimates of treatment effects, i.e. it applies to weight loss (145) as well as to nutraceuticals (146;147).

In **STUDY 1** (Appendix I) we carried out a RCT of 8 weeks in order to explore the clinical efficacy of following an intensive weight loss program compared to a controlled dietary intervention (142).

Eighty obese patients with OA were randomised to either a low-energy diet (LED, n_E=40) providing 810 kcal per day or to a control diet (n_C=40) that provided about 1,200 kcal per day. Patients on LED consumed a Danish food substitute called *Speasy*™, which contained 37% protein, 47%

carbohydrate, and 16% vegetable fat. At baseline, the patients' mean BMI was 35.9 kg/m^2 and mean age was 62.6 years.

Both groups underwent a single dietary counselling session at the onset of the study. The LED group also had a weekly session during the 8-week period. The control group was given a booklet describing weight loss strategies. Changes in body weight and composition were analysed and handled as independent predictors of changes in knee symptoms, and symptoms were monitored using the WOMAC osteoarthritis index (101).

By week 8, both groups had lost a significant amount of weight. Patients allocated to the LED group lost on average 11.1% of their body weight, while those in the control group lost 4.3%, a statistically significant difference (P<0.0001; see figure 3). In parallel to that, at week 8 there was a highly significant 35% improvement in the total (i.e. global) WOMAC scores in the LED group, compared to a non-significant improvement (14%) in the control group (Figure 3).

Independent of group allocation, using linear regression analysis, we determined that 1% weight loss resulted in 2.8 percent improvement of symptoms (total WOMAC), as illustrated in Figure 3.

Interpreting this highly significant effect, following intensive weight loss opposed to control (6.8 %point), it corresponded to a clinical effect size of ES=0.65 [0.20 to 1.10] (P=0.005). The group receiving LED showed a highly significant improvement in the WOMAC-assessed function-score (P=0.0001); there was no corresponding improvement in this score for those on the control diet (P=0.10). Thus, LED resulted in a significant improvement in the WOMAC-assessed function-score compared to the reduction produced by the control diet, ES=0.69 [0.24 to 1.14]; P=0.003. There was a significant improvement in the WOMAC-assessed pain-score within the LED group (P=0.001), whereas no effect was seen after the control diet (P=0.10). However, this difference was of no statistical significance when the groups were compared (ES= 0.33 [-0.11 to 0.77]; P=0.15).

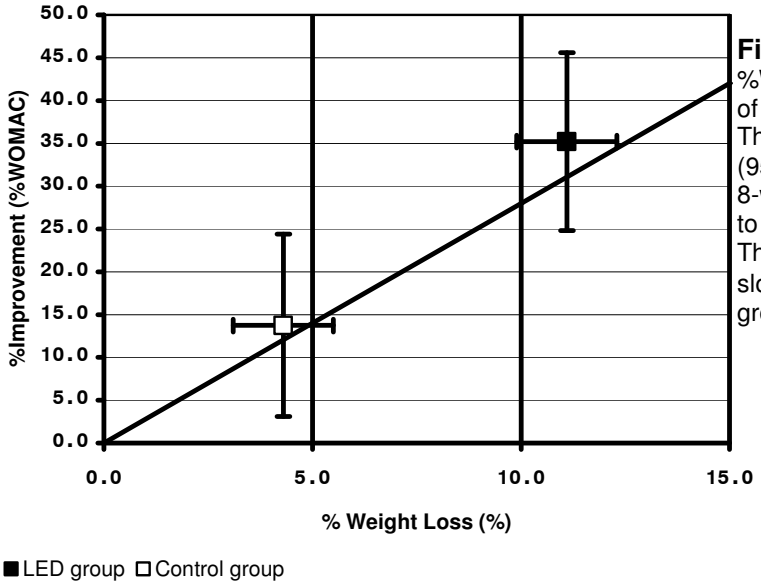

Figure 3: Improvement measured as %WOMAC improvement as a function of weight loss in obese OA patients
The values presented are mean values (95% confidence intervals) following 8-weeks dietary intervention; randomised to either a LED or a Control group.
The line represents the linear regression slope (β=2.8, $\alpha \equiv 0$) – independent of group allocation.

When focusing on the number needed to treat (NNT) with a therapy like weight loss, the results is as follows: Based on those subjects, who showed more than 50% reduction in the total WOMAC index after LED compared to the control diet, the NNT was 3.4 (95% CI: 2.1 to 8.8). If we initiate intensive weight loss therapy in 100 obese patients with knee OA, more than 25 will experience a clinically significant improvement in symptoms after an 8-week period with LED compared to control (142).

As the dropout rate seemed equal between the groups and the reasons for missing data pattern indicated that the data were missing completely at random (MCAR) (148), the risk of making a type 1 error is independent of 'last observation carried forward' bias (149), and the analyses were therefore based on the completers only (i.e. available case scenario) (142). On a *post hoc* level, we published a proceeding of the *World Congress of Pain*, in order to present pain and global disease status, data based on an intention-to-treat analysis (ITT: N_E=44 and N_C=45 (150)). As expected, the magnitude of weight loss decreased in the LED and control group, 9.2% and 2.9%, respectively, with a statistically highly significant group mean difference (P<0.0001). Interestingly, clinical efficacy according to pain reduction was statistically significant when based on the ITT analysis (Δ: 37 mm, P=0.02) instead of completers only. This significant difference corresponded to a clinical efficacy of ES=0.51 (95% CI: 0.09 to 0.93) for pain reduction. The same consequence applied for the total WOMAC index (P<0.0001), indicating a clinically highly significant effect size, ES= 0.94 (95% CI: 0.50 to 1.38) (150).

Following these promising results, we did a systematic clinical review with focus on management of OA in obese individuals, including practical considerations and guidelines for therapy (29;151). In **STUDY 2** (Appendix II) we present a meta-analysis with focus on clinical efficacy following *any* weight loss in overweight patients diagnosed with knee OA (145). We did a systematic review of available RCTs presenting changes in pain and function when overweight patients with knee OA achieve a weight loss. Systematic searches were performed and reference lists from the retrieved trials were searched. RCTs were enclosed in the systematic review if they explicitly stated diagnosis of knee OA and reported a weight change as the only difference in intervention from the control group. OMERACT 3 outcome variables were considered for analysis. Effect sizes and meta-analyses were calculated using the *Cochrane Collaboration* software *Review Manager*. Meta-regression analyses were carried out using weighted estimates from the random effects analyses. Among the 35 potential trials identified, four RCTs including five intervention/control groups met our inclusion criteria and provided data from 454 patients. Pooled ES for pain and physical disability were 0.20 (95% CI: 0 to 0.39) and 0.23 (0.04 to 0.42) at an average weight reduction of 6.1 kg (4.7 to 7.6 kg). Combined estimates are presented in Figure 4. Meta-regression analyses showed that disability could be significantly improved when weight was reduced more than 5.1%, or at the rate of more than a 0.24% reduction per week. Clinical efficacy on pain reduction was present, although not predictable after weight loss. The meta-regression analysis indicated that physical disability of patients with knee OA and overweight diminished following a moderate weight reduction regime. The analysis supported that a weight loss of more than 5% should be achieved within a 20-week period. That is, at least 0.25% per week (145).

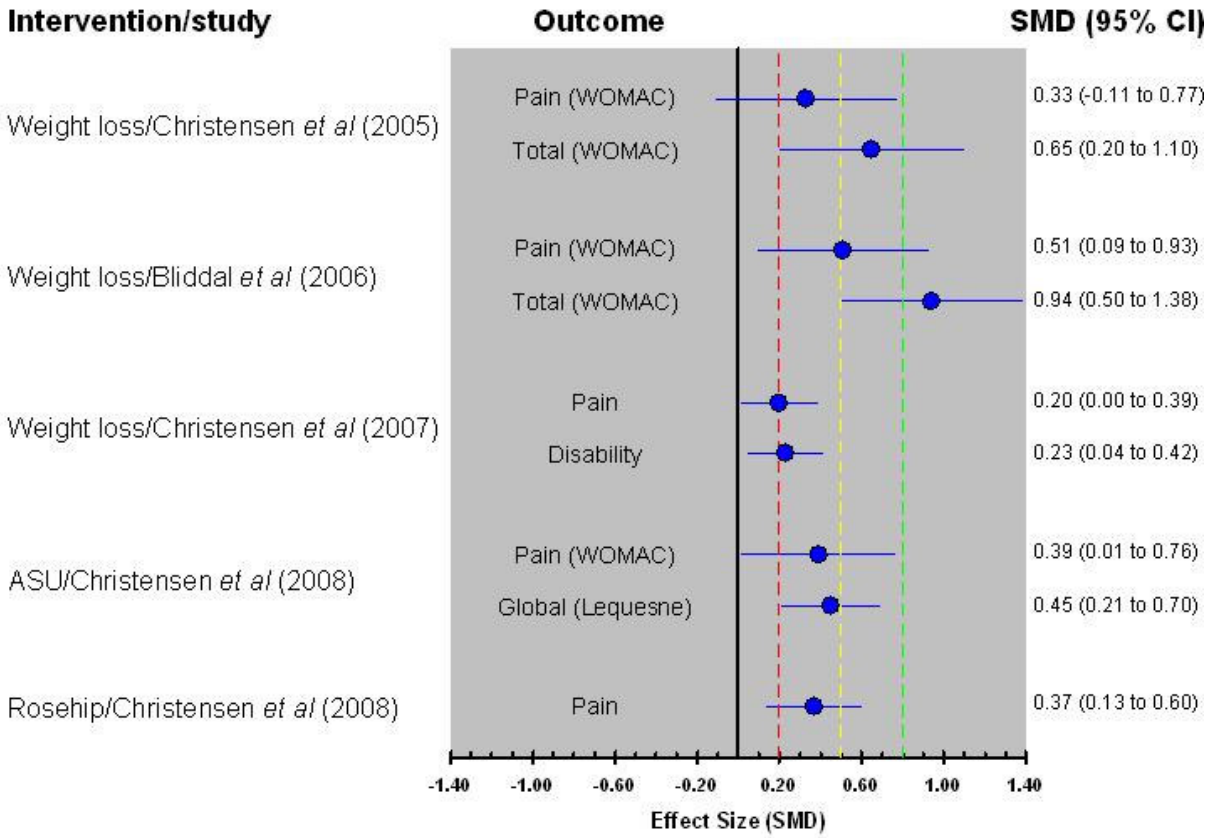

Figure 4:
Results from the 4 included studies in the PhD thesis. An effect size (ES) is the standardised mean difference (SMD) between a treatment group and a control group for an outcome variable - in this case, pain and disability or global/total assessment, reflecting the magnitude of difference between two groups in standardised terms (free of units). *Clinically, an ES of 0.2 is considered small, 0.5 is moderate (and would be recognised clinically), and greater than 0.8 is large*. The Christensen *et al* (2005) and Bliddal *et al* (2006) references refer to the same study (STUDY 1), representing a completer-analysis and an ITT-analysis, respectively.

As illustrated in Figure 2 ('Stairway to surgery'), individuals suffering from OA are often tempted to try one of the many 'alternatives' that are being promoted as a treatment (17;18;152;153). Complementary or alternative therapies (i.e. nutraceuticals) for OA are commonly used, and it is therefore important that health care providers are aware of the evidence supporting the claims. The danger in completely dismissing all 'alternatives' such as nutraceuticals obviously lies in disregarding therapeutic options that may be helpful. This is an issue previously discussed by Edzard Ernst, demonstrating that at least some of these supplements have produced encouraging results in rigorous clinical OA trials (24). One of these is avocado–soybean unsaponifiables (ASU) (154). Essentially, ASU is the fraction of avocado and soybean oil, which, after hydrolysis, is not producing soap. Preclinical studies of ASU have shown some anti-OA properties (154).

In **STUDY 3** (Appendix III) we carried out a systematic review with meta-analysis of the available RCTs applying ASU in the *symptomatic* treatment of OA (146). Our primary aim was to obtain up-to-date evidence-based analysis, which would provide a detailed view of the symptomatic activity of ASU used in the treatment of knee and hip OA. We also wished to investigate possible causes behind the statistical heterogeneity, emphasizing clinical heterogeneity across the included studies (95;124). RCTs from systematic searches were included if they explicitly stated that hip and/or knee OA patients were randomised to either ASU or placebo. The co-primary outcome was reduction in pain and Lequesne index. As a secondary analysis, the number of responders to therapy was analysed as odds ratios (ORs). REML methods were applied for the meta-analyses, using mixed effects models. Four trials - all supported by the manufacturer - were included with 664 OA patients with either hip (41.4%) or knee (58.6%) OA allocated to either 300 mg ASU (n_E= 336) or placebo (n_C=328). Average trial duration was 6 months (range: 3-12 months). Though based on heterogeneous results, the combined pain reduction favoured ASU (I^2=83.5%; ES=0.39 [95%CI: 0.01 to 0.76], P=0.04). Applying the Lequesne index also favoured ASU (I^2=61.0%; ES=0.45 [0.21 to 0.70], P=0.0003). The combined estimates are presented in Figure 4**.** The number of responders allocated to ASU compared to placebo (OR=2.19, P=0.007) corresponded to a NNT of six (4 to 21) patients. These data, combined with the explorative properties from meta-regression analyses, lead us to conclude the following: Based on the available evidence, patients may be recommended to try ASU as a possible treatment for a period of 3 months. Meta-analysis data support better chances of success of treatment in patients with knee OA than in those with hip OA (146).

The last study included in the present PhD thesis is a meta-analysis with focus on an essentially Danish compound. A nutraceutical consisting of a standardised hip powder of *Rosa canina* made from the seeds and husks of the fruits from a subtype of *R. canina* hip powder (i.e. rosehip). Evidence from early *in vitro* studies indicates that *R. canina* hip powder preparations exert anti-inflammatory properties via reduced chemotaxis of peripheral blood neutrophils and monocytes in healthy subjects, and a reduction in CRP is seen after 4 weeks supplementation in patients with OA (155;156). The proposed mechanism of action has been focused on the preparations' anti-oxidative capacities, and a specific galactolipid (called GOPO) has been identified (*in vitro*) as anti-inflammatory, and as such suggested as the possible component behind the preparation's proposed pain reducing property (157). In **STUDY 4** (Appendix IV) we present a systematic review on

clinical efficacy of giving a *R. canina* hip powder preparation for symptomatic treatment of OA based on the available RCTs. Our primary aim was to obtain up-to-date, evidence-based estimates that could provide a detailed view of the potential symptomatic efficacy of *R. canina* compounds in the treatment of OA. We considered the results of such a meta-experiment as crucial for the evaluation of whether or not these preparations would be candidates for future large-scale (i.e., phase III) clinical trials. RCTs from systematic searches were included if they explicitly stated that OA patients were randomised to either rosehip or placebo. The primary outcome was reduction in pain calculated as the effect size, again defined as the standardised mean difference. As secondary analysis the number of responders to therapy was analysed as OR and expressed as NNT. Again, REML methods were applied for the meta-analyses using mixed effects models. The three studies (287 patients and a median trial-duration of 3 months), all supported by the manufacturer (Hyben-Vital International), showed a reduction in pain scores by rosehip powder (n_E= 145 patients) compared to placebo (n_C= 142 patients): ES of 0.37 [95% CI: 0.13 to 0.60], P= 0.002. The combined estimate is presented in Figure 4. With the test for homogeneity supporting that the efficacy was consistent across trials (I^2= 0%), it seems reasonable to assume that the three studies were measuring the same overall effect. It seemed twice as likely that a patient allocated to rosehip powder would respond to therapy when compared to placebo (OR= 2.19; P=0.0009). This corresponds to a NNT of six (95% CI: 4 to 13) patients. The results lead us to conclude that, although based on a sparse amount of data, the results of the present meta-analysis indicate that rosehip powder does reduce pain. Accordingly, it may be of interest as a nutraceutical, although its efficacy and safety need evaluation and independent replication in a future large-scale/long-term trial.

According to the results of the studies included in the present PhD thesis, it seems evident that non-pharmacological treatment of OA may be handled and analysed following evidence-based methods in the same way as these methods are applied for pharmacological therapies. Based on the present evidence and the potential magnitude of clinical efficacy, it seems the only serious choice of treatment to recommend and apply weight loss strategies in obese patients with knee OA before considering taking nutraceuticals. The conclusion on my studies is that weight loss should be the treatment of choice in obese patients with knee OA. Dietary factors on the other hand may be considered as a supplementary or secondary therapy.

PERSPECTIVES

OA is one of the most common forms of musculoskeletal disorders, and any modification of the disease impact is of significant importance for both individual and society. Although no practical disease-modifying agent for osteoarthritis has been identified, the main goal in OA research is to finally reach a therapeutic model, which will create a modification similar to that known from e.g. rheumatoid arthritis with a significant improvement of the condition (158). Prior to reaching this goal, relief of pain and conservation of function must be sought with currently available means, both non-pharmacological and pharmacological, as stated in the EULAR Recommendations 2003 on management of knee OA written by a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT): "*The optimal management of knee OA requires a combination of non-pharmacological and pharmacological treatment modalities*" (17). These European recommendations (2003) explicitly stated that the treatment of knee OA should be tailored according to the individual patient. The expected relative benefits, potential dangers and cost of the intervention must clearly be taken into account. This has relevance to both medical and surgical interventions (17). EULAR stated that non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, insoles, knee bracing) and weight reduction (17), hereby leaving out nutraceuticals. The scientific and medical community remains sceptical regarding the efficacy of dietary interventions for OA despite their broad acceptation by patients (29).

Based on the current meta-regression analysis (145), recommendations for treatment may be given to overweight patients with knee OA. The reduction advocated of at least 7.5% of their body weight obtained with an intensity being at least 0.6% per week would result in a moderate-to-large clinical effect according to self-reported disability (ES=0.67) (145). These results have been included in the recent recommendations for the management of hip and knee OA provided by the *OsteoArthritis and Research Society International* (OARSI)(159). The guideline development committee was asked to indicate their strength of recommendation (SOR) for each accepted proposition on a 0-100 mm VAS. According to their judgement, patients with hip or knee OA, who are overweight, should be encouraged to lose weight and maintain their weight at a lower level (SOR 96%). A weight loss is a core recommendation in 13/14 existing guidelines for the management of lower limb OA (160).

In comparison, SOR only reached 63% when treating with glucosamine. Policy makers and those responsible for public health in the communities should recognise these recommendations.

Clinical trials and meta-analyses have mostly addressed the question of how well a treatment works overall. This evidence, while useful in estimating a population effect, does not lead to advice on how to treat individuals, who often respond differently to treatment (135). To address this diversity, meta-analyses need to evolve from simple pooling to multi-dimensional exploration, creating response surface models to summarize evidence along multiple covariates of interest. For example, the clinician will typically be more interested in the effect of the target joint than a possible association of the condition with the gender of the patient (146). Although tempting, one should omit such explicit analyses in a typical aggregate data meta-analysis (135). Such specific clinical questions may only be answered in a reliable way when applying a so-called individual patient data (IPD) meta-analysis (161). On the contrary, from a statistical viewpoint, trial duration would be characterized as a detailed trial feature (without any error around the estimate, as a consequence of the original RCT study protocol) (137). Applying to all the meta-analyses included in this PhD thesis, a possibility of publication bias with a preference for positive results cannot be excluded (162). In my opinion, the most important limitation associated with the included meta-analyses is the fact that all the included studies on nutraceuticals were funded by industry, which may augment the risk of bias mentioned previously: There is evidence suggesting that trials funded by for-profit organizations may be more positive due to biased interpretation of trial results (163;164). Industry involvement is usually a predictor of more positive results. However, industry control of most aspects of a study does not necessarily affect the credibility of the results. As stated by professor Reginster (in an editorial about the true efficacy of glucosamine) (165), there are several other plausible and legitimate reasons why industry participation may give results that are different from (166) and more positive than those of independent research. Reginster makes a case for funding by industry and thanks the company Rottapharm (Monza, Italy) for funding trials on their own particular form of glucosamine sulphate (165). He adds: "*As is the case with any prescription drug, for glucosamine sulfate, the most relevant clinical trials are those initiated by, participated in, and funded by the pharmaceutical company that has spent years and millions of dollars to study, patent, and develop that particular compound or product, with the numerous concomitant obligations required by the regulatory authorities*" (165). Contrary to this, the elegant meta-analysis from the Boston group by Steven Vlad *et al* must be considered. This group presents explicit estimates

showing that glucosamine is only efficacious when founded by Rottapharm (Monza, Italy) (167). In the meta-analysis of *R. canina* hip powder (STUDY IV), the lack of heterogeneity between studies gives credit to efficacy. The drawback of this observation is - as with the Rottapharm product - that the same company sponsored all three studies on *R. canina* hip powder. Ideally, other similar products from other manufacturers should be tested to substantiate the outcome or even better, the presumed active ingredient (e.g. the anti-inflammatory galactolipid-1 [GOPO]) should be isolated, patented, and tested in a strictly controlled clinical trial following guidelines for Good Clinical Practice (GCP) and consolidated standards of reporting trials (CONSORT) (138). Such initiatives would increase the external validity of any proposed herbal therapy (168).

The results from our studies presented here have lead to associations with international organisations with interest in evidence-based therapy (72). Such initiatives will become of increasing importance for the further progress in rheumatology. The thorough work on weight loss for knee OA is included in many reviews (160) and in treatment guidelines (159). The studies on nutraceuticals, i.e. both the ASU (146) and *R canina* preparations (147), are scheduled to be included in the coming OARSI guidelines and reviews of therapy for OA (Zhang W, personal communication August 2008). The need for bio-statistical approaches to clinical problems is endorsed by many international groups, including the *Cochrane Musculoskeletal Review Group* (CMSG) (169) and the (new) *Cochrane Public Health Review Group* (PHRG) (170). The methods applied and the content handled in this PhD project has the potential to be implemented by the *Outcome Measures in Rheumatology* (OMERACT) initiative (171). Within a typical drug development, a successfully completed development program results in a dossier, a large collection of clinical trial data (phase II and III studies), and other reports. If successful, the package leads to registration, but even during the review process, phase IV studies may have been initiated in order to uncover more effects of the treatment in specialist subpopulations, or perhaps with the object of providing data to cover price negotiations with reimbursers. By analogy to the phase IV of industrial trials, it is time to expand the use of weight loss for knee OA on a large-scale public health format with the objective to provide results, which may justify a large-scale campaign. Medical policy makers are faced with demographic changes amongst which the increasing musculoskeletal disability will threaten the quality of life of the elderly population. Economic evaluation of impact of OA is still uncommon despite the many studies concerning other common diseases. However, it must be understood that the unit purchase price of a drug is not as meaningful

in cost-effectiveness analyses without taking into account the frequency and magnitude of this drug's benefits and adverse effects (172). Musculoskeletal complaints are the most common medical causes of long-term absence, accounting for more than half of all sickness absences lasting longer than two weeks. Musculoskeletal complaints are also very frequently the reason for people to claim disability pensions, and are comparable to the frequency of claims for mental disorders and cardiovascular disorders (1;2). The prevalence of painful disabling knee OA in subjects over the age of 55 is estimated at 10%, out of whom one quarter are severely disabled (5). With about half of these subjects being overweight (62), weight loss should be reimbursed by policy makers (29). By January 2005, the number of Danish citizens being more than 54 years old was 1,520,886 (http://www.dst.dk/), which means that an estimated 75,000 Danish citizens suffer from knee OA with concomitant obesity (151). Total knee arthroplasty (TKA) might be an option (19) and there seems no justification to withhold TKA from obese patients solely on the basis of their body mass index (173). On the other hand, an intensive weight loss strategy should be considered prior to any TKA (29;145). Short-term data suggest a symptomatic improvement following intensive weight loss, at least comparable to what we would expect from knee surgery (142). Epidemiological data consistently show that such weight-loss approaches with a life-long strategy have the potential to stop the cartilage in the knee joint from further deterioration (34;174;175), thus hopefully reducing the expected number of TKA's in the future (19). Even so, scientifically-based advice as gathered by e.g. meta-analyses should be given to the many users of other dietary interventions and supplements, whatever their weight.

ENGLISH SUMMARY

Osteoarthritis (OA) is the most frequent joint disease and the main cause of pain and physical disability in older people. OA describes a common, age-related, heterogeneous group of disorders, pathologically characterised by focal areas of loss of articular cartilage. Obesity and OA co-exist in an increasing part of the population, and there is a tendency towards developing both with increasing age and weight. The objective of this thesis was to describe important non-pharmacological treatments of knee OA with special emphasis on the scientific merits of dietary treatments as evidenced by literature and our own experiments. The methods were to apply the instruments for statistical evaluation of existing literature on non-pharmacological treatment in knee OA, giving a perspective of the importance of patients' self-care in this treatment. STUDY I provided convincing evidence that patients allocated to intensive weight-loss therapy experienced a

moderate-to-large clinical improvement following only 8-weeks of therapy. When combining the existing (sparse) amount of data from randomised controlled trials (RCTs) in a meta-analysis (STUDY II), it was evident that the association between symptomatic improvement and the weight loss showed a clear dose-response relationship; i.e. overweight or obese patients should be encouraged to lose at least 5% of their body weight, achieved within a time-frame of 20 weeks. An alternative is the many dietary components, i.e. nutraceuticals, claiming various pharmacological properties. There is a lot of construct validity associated with improved biomechanics, when overweight individuals lose weight, and this is distinctly different from the effect of nutraceuticals. Avocado/soybean unsaponifiables (ASU) and powder from *Rosa canina* (rosehip) were evaluated, and both products showed promising results towards a reduction of symptoms from OA. STUDY III assessed the efficacy following use of ASU for OA. Though based on heterogeneous results, the combined pain reduction and the Lequesne index favoured ASU when compared to placebo. Based on the available evidence, patients may be recommended to try ASU for around 3 months, and the results indicate a better effect in patients with knee OA than in those with hip OA. The objective in STUDY IV was to assess the potential efficacy associated with use of a patented rosehip preparation, claimed to be evident as a pain reducing agent, although based on vague experimental designs. We concluded that, although based on a sparse amount of data, the results of the meta-analysis indicate that rosehip powder does reduce pain. Accordingly, this compound is of interest as a nutraceutical, and its efficacy and safety need evaluation and independent replication in a future large-scale/long-term trial. It seems evident that non-pharmacological treatments of OA may be handled and analysed as evidence-based as pharmacological therapies. Based on the present evidence, the best recommendation for a person with OA and concomitant obesity is weight loss strategies, while nutraceuticals may be considered as adjunct therapy.

DANISH SUMMARY

Osteoartrose (OA) er den mest almindelige form for ledsygdom, og den er den altdominerende grund til smerte og fysiske vanskeligheder i den ældre del af befolkningen. OA karakteriseres ved at være aldersafhængig og i øvrigt at være kendetegnet ved en heterogen gruppe af patologiske bruskforandringer. Adipositas og OA følges på et befolkningsmæssigt niveau i så høj grad, at vi må forvente at se endnu flere OA tilfælde i fremtiden med denne fænotypiske fællesmængde, da befolkningen bliver både ældre og tungere. Formålet med denne ph.d. afhandling har været kvantitativt at beskrive potentielle nonfarmakologiske behandlinger af knæ OA med udgangspunkt i

eksisterende litteratur omkring kostkomponenter, samt at gennemføre en lodtrækningsundersøgelse for at belyse graden af symptomlindring efter et vægttab. Undersøgelse #1 viste overbevisende, at patienter, der blev allokeret til intensiv vægtreduktion, fik en moderat til stor klinisk bedring efter bare 8 ugers behandling sammenlignet med en kontrolgruppe. For at danne et samlet overblik over den foreliggende (sparsomme) litteratur omkring vægtreduktion til overvægtige patienter med knæ OA, blev undersøgelse #2 initieret - en metaanalyse der illustrerede, at størrelsen af vægttabet er af altafgørende betydning for at kunne garantere patienterne symptomatisk effekt. Således havde undersøgelse #2 det simple budskab, at patienterne skal vejledes, så de taber sig mindst 5% af udgangsvægten, og dette vægttab bør opnås inden for højst 20 uger. Den intuitivt forståelige virkningsmekanisme forbundet med lettere kropsvægt til belastning af et OA knæ er forskellig fra virkningen af diverse kosttilskud (engelsk: nutraceuticals), der på hver deres måde menes at have farmakologiske egenskaber. Metaanalyser af studier af brug af kosttilskud, der ikke tidligere havde været vurderet i en metaanalyse, Avokado-Soja-bønne olie (kaldet *ASU*) og pulveret fra danske hybenbuske (kaldet *Rosehip*), blev inkluderet i nærværende ph.d. afhandling, da disse angiveligt kunne reducere patienternes OA symptomer. I undersøgelse #3 metaanalyseredes den symptomatiske bedring forbundet med brug af *ASU* sammenlignet med placebo. På baggrund af denne metaanalyse konkluderes det, at *ASU* med fordel kan prøves i for eksempel 3 måneder, samt at den eksisterende litteratur i nogen grad understøtter, at knæ OA kan behandles bedre med ASU end hofte OA. I undersøgelse #4 blev de eksisterende undersøgelser af Langelands hyben metaanalyseret for at belyse, hvorvidt den eksisterende litteratur indikerede, at disse *Rosehip* produkter burde testes i et større fase III lignende studie. Det blev konkluderet, at dette *Rosehip* præparats kliniske effekt som smertestillende kosttilskud burde undersøges/bekræftes i en stor uafhængig lodtrækningsundersøgelse. Denne ph.d. afhandling viser, at nonfarmakologiske interventioner til behandling af knæ OA kan håndteres og analyseres præcist ligeså omhyggeligt og metodisk korrekt som det kendes fra den farmaceutiske industri. Baseret på den eksisterende evidens bør den væsentligste anbefaling til den overvægtige del af patienterne med knæ OA være at opnå et mærkbart vægttab initialt ved overvægt eller fedme, mens et eventuelt brug af kosttilskud bør forblive en sekundær overvejelse.

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APPENDIX: study I-IV

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