General discussion
The health status of non-western immigrant groups is usually worse than that of the indigenous population. The prevalence of vitamin D deficiency is high among non-western immigrants. However, vitamin D deficiency is not a disease as such; it refers to a low serum 25-hydroxyvitamin D (25(OH)D) concentration. The relevance of this status depends on its consequences. Low serum 25(OH)D concentrations have been associated with hypocalcemia, rickets and osteomalacia, deep bone pain, growth retardation, skeletal deformities, fatigue, muscle pain, muscular weakness, gait disturbances, and falls and fractures. In addition, it may lead to non-musculoskeletal outcomes such as diabetes mellitus type 1 and type 2, metabolic syndrome, cardiovascular diseases, colorectal cancer, breast cancer, prostate cancer, multiple sclerosis, tuberculosis, schizophrenia and increased total mortality rates. The evidence for causality of the associations between serum 25(OH)D and these non-musculoskeletal outcomes is poor to moderate.

The aim of this thesis was threefold: 1) to estimate the prevalence of vitamin D deficiency among non-western immigrant groups, 2) to estimate the strongest determinants of vitamin D deficiency, and 3) to estimate the association between vitamin D deficiency and consequences, which could be studied well in a general population: muscle strength, muscle pain, functional limitations and diabetes.

Main findings
The main findings of the studies presented in this thesis are:

1) Low serum 25(OH)D concentrations are highly prevalent in adult non-western immigrant populations in the Netherlands, particularly among pregnant women.

Using the conservative threshold of 25 nmol/l, the prevalence of vitamin D deficiency among non-western adults in the Netherlands varied from 51% among Surinamese South Asians to 19% among sub-Saharan Africans (Chapter 2). The prevalence among pregnant non-western women was even higher; being 84% among the Turkish population and 59% among the other non-western groups (Chapter 3). Of the pregnant Turkish women, 22% had a serum 25(OH)D concentration below the 7 nmol/l detection limit. Concentrations below 25 nmol/l are sometimes referred to as severe deficiency, with a threshold of 50 nmol/l for mild deficiency or insufficiency. If this higher threshold is used, the majority of the non-western immigrants in our study populations are vitamin D deficient.
2) Lower serum 25(OH)D concentrations were found in non-western immigrant populations compared to indigenous European populations and compared to non-western populations in their countries of origin.

Other studies in Europe (Chapter 4) have found similar low serum 25(OH)D concentrations in non-western immigrant populations to those found in the Netherlands (Chapters 2 and 3). In Turkey and India, some groups had low serum 25(OH)D concentrations, but others had serum 25(OH)D concentrations similar to or higher than the concentrations among indigenous European populations.

3) Oral vitamin D was the greatest modifiable contributor to serum 25(OH)D concentrations among a multiethnic population in the Netherlands.

The consumption of fatty fish and the use of supplements containing vitamin D were the greatest modifiable contributors of the serum 25(OH)D concentration (Chapter 2). These determinants were followed in importance by area of uncovered skin, use of tanning bed, consumption of margarine and preference for sun. Thus, both dietary and ultraviolet exposure determinants were associated with serum 25(OH)D concentration. However, the associations between serum 25(OH)D concentration and non-modifiable determinants such as ethnic group, season and pregnancy or breastfeeding were stronger than the associations with modifiable determinants. Exposure to sunlight and dietary intake were both associated with serum 25(OH)D concentrations in the studies in Europe and the immigrants’ countries of origin described in Chapter 4.

4) Associations between vitamin D deficiency and muscle strength, muscle pain, functional limitations were ambiguous.

Several measurements to assess muscle-related outcomes were performed among a multiethnic adult population in the Netherlands: handgrip strength, chair stand test, self-reported muscle pain in the upper legs and shoulders, and self-reported functional limitations in standing from a chair, climbing stairs and walking a few hundred metres (Chapter 5). The associations between serum 25(OH)D concentrations and these muscle-related outcomes were ambiguous; e.g. the regression coefficient (95% Confidence Interval) for the association between serum 25(OH)D and handgrip strength adjusted for age, BMI and ethnic group, was -2.53 (-5.32 – 0.27) for men and 0.69 (-0.76 – 2.13) for women.
5) A non-significant association between vitamin D status and diabetes was found. Self-reported diabetes mellitus was defined as positive answers to two questions: having diabetes mellitus, and using medication for diabetes. Diabetes mellitus was defined as self-reported diabetes mellitus or fasting glucose ≥7.0 mmol/l. Although not significantly, prevalence of diabetes mellitus was higher among individuals with lower serum 25(OH)D concentrations – adjusted for age, gender, ethnic group, BMI and season – compared to individuals with higher serum 25(OH)D concentrations (Chapter 6). Odds Ratios (95% CI) were 1.70 (0.60 – 4.81) for serum 25(OH)D < 25 nmol/l and 2.13 (0.79 – 5.77) for serum 25(OH)D ≥25 nmol/l; <49 nmol/l, compared to the reference group (serum 25(OH)D ≥50 nmol/l). However, the estimated associations (Odds Ratios) were high enough to suggest that lower serum 25(OH)D concentrations might be associated with diabetes mellitus.

Non-western immigrants
In Dutch, we used the term “niet-westerse allochtonen” (literally: non-western allochthonous individuals) to identify non-western immigrants. An “allochtoon” is defined as someone ‘who comes from another country’. In the Netherlands this term is commonly used – as counterpart of the “autochtoon” (literally: autochthonous individual; indigenous individuals). Non-western immigrants, refers to persons who themselves immigrated from a non-western country (first generation immigrants). However, as we did not make this generational distinction, the use of the term “non-western immigrants” for our study population is not entirely accurate, but the best available.

The term multiethnic is also used in articles and chapters in this thesis. This term is suitable for the total study population, as we included groups of indigenous Dutch or western individuals who do not belong to the group of non-western immigrants.

Ethnicity is a concept without a generally accepted definition. It refers to a people or tribe. It implies one or more of the following: shared origins or social background; shared culture and traditions that are distinctive, maintained between generations, and leading to a sense of group identity; and a common language or religious tradition. Self-perceived ethnicity is not definitions-based, varying between individuals and over time; some people may also have multiple self-perceived ethnicities. In a country or region, ethnic differences in health can be explained by five mechanisms: genetic factors, migration processes, culture or acculturation, socio-economic position and social context. Ethnicity is difficult to assess. Often, ethnicity is based on countries of birth of the participant and of his or her parents. In the study among adults (chapters 2, 5 and 6), self-reported countries of birth and the Statistics Netherlands’ definition were used: a person is Dutch if both parents were born in the Netherlands; if only one parent was born in the Netherlands, the person’s ethnic group is based on the other parent’s country of birth; if both parents are
born abroad, the mother’s country of birth defines the person’s ethnic group. The advantages of this definition for assessing the prevalence of vitamin D deficiency are that 1) it is easy to assess, 2) it is relatively easy to generalise because, at least in the Netherlands, the total number of inhabitants from ethnic groups based on countries of birth is known, and 3) when prevalence is high in a certain group, this group is relatively easy to identify for a public health intervention.

However, it is clear that this definition based on countries of birth only refers to a part of the concept of ethnicity, and is far from complete. Secondly, it is rather arbitrary especially in individuals with mixed origins. Thirdly, an ethnic group based on countries of birth can still be far from homogeneous, which can result in unnoticed differences between subgroups. For instance, immigrants from Suriname may originate from India (South Asian), Africa (Creole), or other parts of the world. These subgroups differ in their skin type, culture, food habits etc. Therefore, the Surinamese immigrants in the study of adults (chapter 2), were asked whether they belonged to the Surinamese South Asian, Surinamese Creole or some other population. In the study of pregnant women (chapter 3), only self-reported ethnicity was known. For the literature study (chapter 4) we had to use the ethnic group as presented in each articles. Labelling the specific ethnic groups can also be done in various ways. Two publications describe meaning, strengths and weaknesses and give comments and recommendations of several terms such as white, European, western, Caucasian, negro, black, and African American. It is advised to abandon the terms white, Caucasian, western and indigenous. For instance, the weakness of western is that it is not geographically specific, and that it is used to describe heterogeneous populations. This same argument is used for some terms used to describe populations of African origin such as black and African. However, in our studies, the terms western and sub-Saharan African were used. These terms were suitable as the individuals in the study population came from these broad geographical locations. Separating these groups into more refined categories according to specific countries of origin would have made the groups too small for analysis.

The sub-Saharan African population that was studied (chapters 2, 5 and 6) was heterogeneous with regard to countries of origin, which can influence their vitamin D states. For instance, individuals from Somalia are predominantly Islamic, meaning Somali women more often wear veils, thereby decreasing exposure to sunlight and vitamin D synthesis, whereas individuals from Ghana are more often Christian, thus not wearing veils. To assess the relative contribution of vitamin D deficiency determinants, we wanted to include a group of individuals with the darkest skin type, in addition to the groups we studied because they form the largest non-western populations in the Netherlands (Turkish, Moroccan and Surinamese immigrants). Because of the variation within the determinants studied to identify associations with serum 25(OH)D concentration, it was preferable to include a heterogeneous population such as sub-Saharan Africans.
Adults
Adults aged 18-65 years were studied as the number of elderly non-western immigrants in the Netherlands is low. As of 1 January 2003 – the start of our study – only two percent of the non-western immigrant population in the Netherlands was over 65 years of age (approximately 40,000 individuals), while fifteen percent of the indigenous Dutch and western immigrant population was 65 or older. As of 1 January 2009, the ratios were four percent among non-western immigrants and sixteen percent for indigenous Dutch and western immigrant populations. It is expected that the number of elderly non-western immigrants will rise further. Vitamin D deficiency has long been recognized as highly prevalent among the elderly. In the elderly, the skin becomes thinner, being less able to produce vitamin D upon exposure to sunlight, and kidney functions decrease, resulting in a lower capacity to hydroxylate 25(OH)D into the active metabolite 1,25(OH)2D. Among the elderly, severe vitamin D deficiency leads to osteomalacia, muscle weakness, and a higher incidence of falls and fractures. The effects of vitamin D deficiency may increase as the non-western immigrant population ages. The problem might be further compounded as many non-western immigrants will have been suffering from vitamin D deficiency for much longer than their indigenous western counterparts.

Study limitations
Except for the literature overview presented in chapter 4, we needed to take a sample to collect data to answer the study questions (chapters 2, 3, 5 and 6). It proved difficult to recruit non-western immigrants and perform valid measurements. The difficulties performing these kind of studies are discussed here:

Drawing the sample
For the studies presented in chapters 2, 5 and 6, a population sample was needed. As it was planned to measure height, weight, and muscle strength, and obtain blood samples, we planned to perform the measurements at general practitioners’ practices. To stimulate attendance, we preferred that participants be invited by their own general practitioners. The less practices that were needed, the more feasible the study would be. As a random sample from municipal registries would lead to a high number of general practitioners, we chose the general practitioners’ practices ourselves and drew our sample from their patient files. The difficulty with this approach is that patient files do not record ethnicity. Potential solutions for not having ethnicity data available are e.g. 1) a mailing to all individuals in the files with questions to assess ethnicity, 2) a match between the patient file and the municipal registry to assess ethnicity, 3) drawing an initial sample then assessing ethnicity at a later time, and 4) drawing a sample based on estimated ethnicity (e.g. family names or the general practitioner’s knowledge) combined with a later assessment of ethnicity.
The disadvantage of the first option is that it takes too much time and effort; of the second that it may run contrary to privacy legislation. As we were interested in the prevalence of vitamin D deficiency in the largest immigrant ethnic groups, the third option was not suitable. Therefore, we chose option four. The general practitioners, who estimated ethnicity for drawing the sample, did not assign all their patients to the ethnic group as later established through the questionnaire. Nine percent of the study participants were from ethnic groups other than the six originally selected.

Response
A high response rate is a necessary condition for a valid conclusion of prevalence rates. Non-western immigrants are considered as ‘groups that are difficult to contact’. They often change residence, resulting in a higher risk of errors in the source databases; a larger proportion of them is illiterate, resulting in a lack of response to written invitations. Frequent change of (mobile) telephone numbers results in out-of-date numbers and there is a certain unwillingness to participate in studies specifically among non-western immigrants because they do not want their ethnic groups to receive negative attention. Another experience from the study presented in chapters 2, 5 and 6 was that some specific groups of non-western immigrants had – more so than the indigenous Dutch – problems with the drawing of blood for the study.

The two studies that we performed for estimating the prevalence of vitamin D deficiency (chapters 2 and 3) met rather low response rates. In both studies, the reasons for non-response were studied to try to identify whether selection bias had occurred. In the study among pregnant women (chapter 3), serum 25(OH)D concentrations were available for only 47% of the eligible women. Identifiable reasons for this low rate were that some women came to the midwives’ practice during a late stage of their pregnancy, had already undergone the standard blood test in another healthcare setting, or both. Other possible reasons for this low figure are that the midwives 1) did not add the vitamin D test to the standard blood test, 2) did not receive the results from the laboratory, or 3) did not record the serum 25(OH)D concentration in the medical files. A definite conclusion about the occurrence of selection bias could not be drawn. However, it was argued that even if none of the women with an unknown serum 25(OH)D concentration were vitamin D deficient, 25% of the total population would still be vitamin D deficient: such a situation would still be a major problem.

Although several efforts were made to increase the response rate of the study in the general population (chapter 2, 5 and 6), the response rate was somewhere between 28% and 50%. Individuals who were in the sample, but did not participate in the study, were asked to complete a short questionnaire as to the reason for not participating, which included some questions on determinants of vitamin D deficiency. However, the majority of the non-participants did not complete the non-response questionnaire, making it impossible to estimate possible selection bias.
Study design
The study which was performed to assess the prevalence of vitamin D deficiency among adult non-western immigrants in the Netherlands (chapter 2) had a cross-sectional design. The data from this study were also used to answer the study questions relating to two consequences of vitamin D deficiency: muscle related outcomes and diabetes (chapters 5 and 6). Due to the cross-sectional design, a conclusion on the causality of a relation between vitamin D and the consequences could not be drawn.

Questionnaire
A difficulty faced in questionnaire design is that questions can be interpreted differently based on ethnic perceptions or socio-economic positions, thereby introducing bias. Therefore, it is important that the questionnaire be validated among a similar population as the study population.

In the study among the adult multiethnic population in the Netherlands (chapters 2, 5 and 6) a questionnaire was used to measure general characteristics, exposure to sunlight, dietary intake and muscle related complaints. To our knowledge, no questionnaires for these measures have been validated among non-western immigrant populations. The questions used were based on questionnaires from other studies and pre-tested for validity. In the pre-tests, a “migrant peer educator” (in Dutch: Voorlichter in Eigen Taal en Cultuur, VETC’er) asked non-western subjects with a low but sufficient educational level to complete the questionnaire, and discussed the reported answers with the subjects. The pre-test resulted in changes of the questionnaire. For example, we asked how much time someone spent outdoors. In some non-western immigrant populations, being outdoors is interpreted as not being at home, so including time spent inside other houses or buildings (e.g. visiting others); being on the balcony at home is not regarded as being outdoors. As vitamin D is related to the exposure to sunlight, the question was changed, making it clear that the time outdoors “in the open air” was meant.

Another difficulty with the questionnaire was the consumption of fatty fish. The fat-content of several types of fish sold at the ‘Haagse markt’ (The Hague market), where many non-western immigrants in The Hague do their shopping, is not known. Therefore, only some fatty fish could be used as examples in the questionnaire. It is possible that the examples were more suitable for some ethnic groups than others.

Treatment
As the prevalence of vitamin D deficiency among non-western immigrants is high, doctors should realize the high probability of vitamin D deficiency among their patients. A portion of the female patients in the study in The Hague, of whom 82% were vitamin D deficient (serum 25(OH)D < 25 nmol/l), had muscle complaints, diffuse pain or fatigue. Although
these complaints are too general to point to vitamin D deficiency as the sole cause, it might play a role in a large proportion of patients presenting these complaints. A study in Great Britain observed that family screening was effective in identifying undiagnosed Asian vitamin D deficient individuals. Taking into account the high prevalence of vitamin D deficiency in the Netherlands, it might be effective there too. A disadvantage of this method is that vitamin D deficient family members may not experience the negative consequences thereof, and serum-concentrations might be treated instead of patients. However, the fact that these people have not yet visited a doctor themselves does not mean they do not experience consequences of vitamin D deficiency. Muscle complaints, diffuse pain and fatigue due to vitamin D deficiency will probably not occur at once, but gradually, and individuals may get accustomed to them.

To treat vitamin D deficiency, several dosages of vitamin D have been proposed. Holick made an overview of the advised dosage for children and adults, according to the cause of deficiency. However, patient adherence may not be optimal, e.g. patients who do not get a repeat prescription. As calcium is also important (e.g. for bone health), practitioners should prescribe calcium or advise the use of dairy products to vitamin D deficient individuals with an insufficient intake of calcium.

**Prevention**

Vitamin D deficiency can be prevented by increasing exposure to direct sunlight, increasing the consumption of foods rich vitamin D, using oral vitamin D supplements, fortifying foods with vitamin D, or a combination of the above. These options are discussed below.

**Increasing exposure to direct sunlight**

It is often said that exposure to sunlight is the strongest source of vitamin D. However, it is not known whether this holds true for non-western immigrants at higher latitudes. They generally have a darker skin than the indigenous population and therefore need more sunlight to produce the same amount of vitamin D. Nutritional determinants and supplementation, rather than sunlight-related determinants, were found to be the greatest modifiable contributors to serum \( 25(\text{OH})D \) concentration in the adult multiethnic population (chapter 2). However, season – a non-modifiable determinant – was found to be strongly associated with serum \( 25(\text{OH})D \) concentration. This implies that exposure to sunlight is a relevant determinant of serum \( 25(\text{OH})D \) concentration in an adult multiethnic population in a northerly country such as the Netherlands.

Reasons for avoiding sunlight mentioned by focus groups of Turkish women were: the association with skin cancer, allergy, migraine, and religious reasons. Another reason for avoiding sunlight might be the desire to have a light skin, e.g. among the Surinamese South Asian population. Skin cancer is a consequence of the same ultraviolet radiation needed
for the production of vitamin D; DNA damage occurs continuously while the production of vitamin D decreases after a certain amount of sunlight exposure as production shifts instead to non-active metabolites (e.g. lumisterol). Both the amount of DNA damage and the production of vitamin D is dependent on skin type. Individuals with the darkest types of skin are at the least risk in terms of DNA damage and skin cancer from exposure to sunlight, but also receive the least benefit in terms of vitamin D production.

For several non-western immigrants, “allergy to sunlight” was a mentioned reason for not participating in a study to compare three treatments of vitamin D deficiency, where the exposure to sunlight was one of the treatments (personal communication, P. Lips). The prevalence of diagnosed sunlight allergy is not so high that all of these potential participants really were expected to be allergic. However, whether the allergy is real or not, advice to expose themselves to sunlight will probably not be effective for this group.

An advantage of using sunlight exposure for the prevention of vitamin D deficiency is that toxic concentrations of serum 25(OH)D will not occur, as other metabolites will be produced instead of vitamin D as serum 25(OH)D concentrations rise. However, if exposure to sunlight is chosen as a method to increase serum 25(OH)D concentrations among non-western immigrants, attention should be paid to the socio-cultural barriers and to the adverse effects of an increased exposure to sunlight.

Increasing the consumption of foods rich in vitamin D

Fatty fish, such as herring, salmon, and mackerel, are a natural source of vitamin D. In the Netherlands, the recommendation is to consume two portions of fish a week. It is not known whether the fish consumed by non-western immigrants is fatty fish. Our data teach us that the consumption of fatty fish was, relatively, the greatest modifiable contributor to serum 25(OH)D concentration in an adult multiethnic population (chapter 2).

Turkish female participants in focus groups were positive about increasing the consumption of fatty fish as it is a natural source of vitamin D. However, mentioned barriers were the amount of work required to prepare fish, the smell, and other family members who do not like the taste of fish. Vegetarianism, which is expected to be common among the Surinamese South Asian population, is another barrier to increasing the consumption of fatty fish.

Other, non-fortified food sources of vitamin D are liver (pork liver ≈ 1 µg /100 gram portion; beef liver ≈ 0.2 µg/100 gram portion) and eggs (≈ 1 µg/egg). These products are generally not consumed to guarantee a substantial intake of vitamin D.

Increasing the use of oral vitamin D supplementation

Vitamin D can be supplemented preventatively, as well as for treatment purposes. However, without a diagnosis of deficiency, the recommended upper limit of daily intake should not be exceeded. In the Netherlands, the current daily intake limit is 50 µg for individuals older than
one year. The European Food Safety Authority has set this same upper level for individuals older than ten years.

Several researchers have mentioned supplements as the recommended method to increase serum 25(OH)D concentrations for populations at risk of vitamin D deficiency. Vitamin D supplements appeared to be one of the greatest modifiable contributors in our study among an adult non-western population (chapter 3). The attitude towards vitamin D supplements among Turkish females in focus groups was negative: they thought that the use of these supplements might lead to them becoming overweight or suffering effects of toxicity, that a doctor should be consulted before using supplements, or that supplements could only be used on a doctor’s prescription after the diagnosis of vitamin D deficiency. These attitudes were confirmed by intercultural project workers in an expert group. They also mentioned that it was hard to understand that overweight individuals could be deficient. Furthermore, individuals from non-western origin may see vitamins as something additional, rather than as necessary supplement. Immigrants from African countries might not accept advice to use vitamin supplements if it is not reimbursed by the insurance company. In the Netherlands, vitamin supplements are not reimbursed.

The Health Council of the Netherlands has recently (October 2008) advised supplement use for several groups at risk for vitamin D deficiency. These risk groups are presented in table 1.

Table 1. Risk groups for vitamin D deficiency which are advised to use vitamin D supplementation by the Health Council of the Netherlands.

<table>
<thead>
<tr>
<th>Daily 10 µg (400 IU) vitamin D extra</th>
<th>Daily 20 µg (800 IU) vitamin D extra</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Children aged up to four</td>
<td>- People who have osteoporosis</td>
</tr>
<tr>
<td>- People aged between four and 50 (women) or 70 (men) with dark skin, who do not spend enough time outdoors</td>
<td>- People who live in a care home or nursing home</td>
</tr>
<tr>
<td>- Women aged up to 50 who wear a veil</td>
<td>- People aged over 50 (women) or 70 (men) with dark skin or who do not spend enough time outdoors</td>
</tr>
<tr>
<td>- Women who are pregnant or breastfeeding</td>
<td>- Women aged over 50 who wear a veil</td>
</tr>
<tr>
<td>- People aged over 50 (women) or 70 (men) with light skin</td>
<td></td>
</tr>
</tbody>
</table>

Some individuals are sensitive to vitamin D intoxication, especially those with sarcoidosis, tuberculosis or lymphoma, because the hydroxylation into 1,25-dihydroxyvitamin D is increased in these patients, leading to hypercalcemia. If preventative supplementation is being suggested, these patients should be advised not to take the supplements or to only do so when combined with the monitoring of their serum calcium concentration.
Fortifying foods with vitamin D

In the Netherlands, margarine is fortified with 7.5 µg vitamin D per 100g. From 1961, it was mandatory to fortify all margarines with vitamin D. In 1999, the mandatory fortification was replaced by a covenant between margarine producers and the Ministry of Health. The policy of fortification, and thus the availability of products fortified with vitamin D, differ by country.

Milk products, cereals and orange juice are fortified with vitamin D in several countries, and the production of fortified cheese and enriched mushrooms is described in literature. A comparison between countries with various fortification policies revealed that vitamin D intake was highest in countries with some mandatory fortification of staple foods such as milk and margarine, and lowest in countries with no mandatory fortification of foods, and limited or restricted food fortification (including the Netherlands, despite the fortification of margarine).

Before fortification of foods is allowed, the risk of exceeding the upper tolerable limit has to be evaluated. The National Institute for Public Health and the Environment in the Netherlands has calculated a maximum level of 4.5 µg per 100 kcal of food for fortification with vitamin D. This is a temporary situation, in anticipation of forthcoming European legislation.

To promote fortification of foods for preventive aims, one should consider what products are consumed by which people. Non-western immigrants are at increased risk of vitamin D deficiency; all non-western immigrant groups, although not always significantly, consumed less margarine – which is fortified in the Netherlands – than the indigenous Dutch group (chapter 2). Milk has the disadvantage that many individuals, particularly from non-western populations, are lactose-intolerant. The Turkish female participants in focus groups judged fortification of oil as a good option to improve vitamin D status, as they prefer oil to margarine. The arguments against the consumption of margarine were that it might contain animal fat (indicated by the yellow colour), that it contains additives (E-numbers mentioned on the packing), and that they thought it had a greater association with becoming overweight than oil.

When mandatory fortification is being considered, ethical aspects are also at stake, as it could be regarded as mass medication. For optional fortification, it is difficult to predict which products will be fortified. Furthermore, it is important that the at-risk groups consume the fortified products, but it is possible that fortified products will be more expensive than the non-fortified ones and as the non-western immigrants generally have lower incomes, they might choose the non-fortified variants.

A combination of the above methods

Due to the small regression coefficients for the association between the modifiable determinants and serum 25(OH)D concentration, a combination of methods was recommended (chapter 3). The effectiveness of launched interventions should be evaluated,
both on serum 25(OH)D concentrations and on consequences of vitamin D deficiency. The opinion that vitamins are not harmful is not always true. For instance, supplementation with β-carotene (pre-vitamin A) and α-tocopherol (vitamin E) appeared to be more harmful among cigarette smokers. \(^6\) β-Carotene treatment did not result in a decrease in cancer at any of the major sites but rather in an increase at several sites, most notably lung, prostate and stomach. The vitamin E group had fewer incident of prostate and colorectal cancers compared with the group not receiving vitamin E, but more cancers of the stomach.

**Conclusion**

Vitamin D deficiency is highly prevalent among non-western immigrants compared to indigenous European populations. Vitamin D deficiency is particularly common in pregnant non-western immigrant women. Of the modifiable determinants, fatty fish and supplements were the greatest contributors to the serum 25(OH)D concentration in a multiethnic population. Unambiguous associations between low serum 25(OH)D concentrations and muscle strength, muscle pain and functional limitations were not found in the study described in this thesis. We did find an association between low serum 25(OH)D concentrations and diabetes mellitus, though this was not significant. Several studies found negative consequences of low serum 25(OH)D concentrations. Hence, general practitioners, midwives and other medical personnel should be alert on the possibility of vitamin D deficiency among non-western immigrants.

**Recommendations for further research**

Three questions remain to be answered by further research.

A. What are the consequences of low serum 25(OH)D concentrations in non-western immigrants?

In the studies described in this thesis, the association between serum 25(OH)D concentration and consequences (muscle strength, muscle pain, functional limitations and diabetes mellitus) were studied in a cross-sectional design. In order to assess possible causality of the associations, a longitudinal design is necessary. Such a longitudinal study could be an observational or an intervention study. A lack of variation in serum 25(OH)D concentrations in the non-western participants might be the reason for not finding clear and significant associations in the studies presented in this thesis. Therefore intervention studies are recommended to study the consequences of low serum 25(OH)D in non-western immigrants. In the case of pregnant women, the consequences include those in their offspring.
B. How can serum 25(OH)D concentrations be raised in non-western immigrants?
There are indications that the low serum 25(OH)D concentrations in non-western immigrants are harmful. The most effective strategy to raise those concentrations is not known. The Health Council of the Netherlands’ advice to supplement risk groups with vitamin D should be evaluated to assess its effect. Furthermore, comparative studies are recommended in which various strategies are used to reach non-western immigrants and to increase their vitamin D intake, exposure to sunlight, or both.

C. How can vitamin D intake and exposure to sunlight by non-western immigrants be measured in a valid way?
This is a methodological issue. A validated questionnaire to assess vitamin D intake and exposure to sunlight in non-western immigrants was not found. A validated questionnaire or other possible instruments would enable us to measure the real intake or exposure validly, making the results of future studies on vitamin D in these groups more valuable.
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