

The Contribution of Acupuncture  
and Moxibustion to Healthcare,  
an Evidence-based Approach



Ineke van den Berg-de Lange

# The Contribution of Acupuncture and Moxibustion to Healthcare, an Evidence-based Approach

针灸与艾灼对于保健的贡献：一个以实证为基础的方法

*De bijdrage van acupunctuur en moxa-therapie  
aan de gezondheidszorg, een op bewijsmateriaal  
gebaseerde benadering*

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Chapter

I

**Prologue and General  
Introduction**

## PROLOGUE

Complex pain problems, prevention of injuries and recurrent complaints, as well as complementary care related to pregnancies, take an important place in the daily practice of physical therapy. More than 32 years ago, when I was searching for more treatment modalities in my practice as a physiotherapist, I came into contact with classic acupuncture through an acupressure training program: 'Shiatsu according to Tokujiro Namikoshi' and learned that this form of preventive healthcare already has been in existence for more than 3,000 years. Inspired, I studied acupuncture for six years, according to traditional Chinese medicine and Chinese herbal medicine, while continuing to practice as a physiotherapist. After an extra traineeship in China I was awarded my 'Bachelor's Degree in Acupuncture and Chinese Herbal Medicine'.

Since 1988, I have increasingly applied the knowledge and skills I obtained in the area of acupuncture and Chinese herbal medicine in my own practice and in the process, it became clear to me that it yielded very good results in many of my patients. Patients deserve the best of both worlds when it comes to their health. Ideally healthcare blends the best of both worlds by offering patients healthcare options from the perspective of both Western and complementary medicine. During the acupuncture treatment sessions, but also during my standard consultations with general practitioners, I spoke with many of them (the patient, her companion, and her GP) about integration of traditional Chinese medicine in Western healthcare. From these discussions it became clear that there is a significant amount of distrust regarding the application of acupuncture and moxibustion or, for that matter, complementary medicine in general. This distrust may be largely ascribed, I believe, to the 'unknown, unloved' phenomenon. The lack of (Dutch) evidence-based studies about the efficacy of the use of acupuncture is likely to be a major contributing factor.

In view of my positive experiences and the good results reported by the patients themselves, I felt more and more driven to reduce this distrust. After much deliberation, I did so in two ways: first, by performing studies in an academic setting that would enable the translation of evidence-based research into evidence-based practice, and secondly, by establishing a

scientifically recognizable and thus more reliable position for complementary medicine. The question I asked myself was, "Would it be possible in the Netherlands to conduct and report scientifically sound studies in the area of complementary medicine?"

The answer came from the field of epidemiology. Knowledge in this area is indispensable in order to address questions related to traditional medicine in a sound manner. The field of epidemiology is concerned with the frequency with which diseases occur and the (causative) factors that might be implicated. This discipline sees the human being as one whole organism, rather than the sum of many separate organs, and disease as a multifactorial complex process. Furthermore, methodology is the very essence of this type of research. Central in *clinical* epidemiology is quantification of the effects of diagnostic tests and of treatment as well as establishing an individual's risk for the occurrence of disease or its progression. Note that epidemiologists do not devise new diagnostic tools or treatment methods, but rather quantify the benefit of using them. This is of interest not only to the physicians and therapists, who develop or apply treatments, but also to policymakers - and of course the patient.

The importance of synergy between modern medicine and complementary health care and the clinical value of blending these disciplines appeals greatly to me. I aim to identify the strengths and limitations of acupuncture and moxibustion, as described in Traditional Chinese Medicine, and evaluate how these therapies can be implemented in modern medicine, taking the perspective of patients, physicians, complementary therapists, health insurers, and healthcare policymakers.

## GENERAL INTRODUCTION

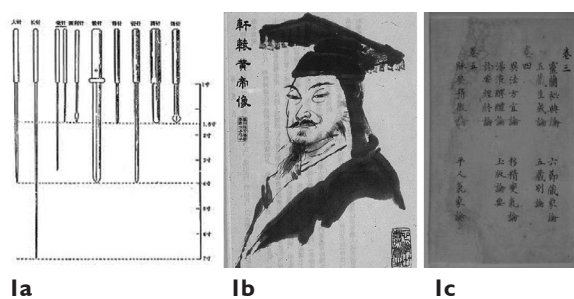
Although recent international publications have featured articles describing the effectiveness of Traditional Chinese Medicine (TCM), little has been published about the implementation of TCM in today's healthcare in the Netherlands. In this thesis, we tried to bridge this gap and interpret how TCM, and specifically acupuncture and moxibustion, can demonstrate its value in today's medicine as it is practiced in a Western country. To accomplish this aim we used a range of epidemiologic techniques leading to evidence-based results.

In this introduction we will first describe acupuncture and moxibustion and review fundamental research of the working mechanisms.

### Acupuncture

Acupuncture is one of the components of TCM. It can be described as the ancient practice of piercing specific points of the body with fine needles that are applied to relieve pain, to induce surgical anesthesia, and to serve therapeutic purposes<sup>1</sup> (Figure 1). The use of acupuncture is based on more than 3000 years of experience and study. Indeed, the oldest surviving book about acupuncture, the *Hungdi Neijing Suwen*, was published in 200 BC. It systematically describes a wealth of detail in patient care and cure<sup>2</sup>.

Figure 1



1a. Needles used in ancient acupuncture

1b. Huang Ti, the Yellow Emperor. According to Chinese legend he is the third of the first emperors in Chinese history. The beginning of Huang-ti's reign, traditionally given as 2697 BC (when Huang-ti was 7 years old), is usually taken as the beginning of Chinese history.

1c. Huangdi Neijing (黄帝内经), also known as 'The Inner Canon of Huangdi or Yellow Emperor's Inner Canon', is an ancient Chinese medical text that has been treated as the fundamental doctrinal source for Chinese medicine for more than two millennia and until today.

### Moxibustion

Moxibustion involves burning the herb Mugwort (*Artemisia Vulgaris*) either directly on the skin or indirectly over acupuncture points, which decreases inflammation by increasing white blood cell count in the area (Figure 2). The acupuncturist selects certain acupuncture points, modalities and Chinese herbs, depending on which TCM-syndrome type presents itself. For instance, if the TCM diagnosis is Cold dominate Bi syndrome, like in rheumatoid arthritis, moxibustion is the preferred choice.

Figure 2 Moxibustion



2a Common Wormwood. (*Artemisia vulgaris* LINN.)

2b Moxa rolls as used in general acupuncture practice

2c Subject: Moxa burning of foot. Artist: Kunisada Utawaga (1786-1864)

Acupuncture, (针灸: zhēnbiān), or acupuncture together with moxibustion (针灸 zhēnjiǔ)<sup>5</sup> is not, nor has it ever been, a complete singular and independent system of medicine. In addition to acupuncture, the whole spectrum of TCM embraces many other forms of healing, such as Chinese herbal medicine, moxibustion, exercise, diet, and massage. Although banned by law in China at the beginning of the 20th century, TCM continued to be practiced as folk medicine until Mao Tse-tung (毛澤東) reintegrated TCM into China's health care. President Nixon's visit to China in 1972 encouraged the Western interest in acupuncture, which in turn led to a significant growth in the study and practice of evidence-based acu-

puncture. Several reports have indicated the effectiveness of acupuncture when used to treat many conditions that often do not respond to conventional treatment – such as chronic neck and lower back pain, knee and hip osteoarthritis, epicondylitis lateralis, and fibromyalgia<sup>6-18</sup>. Furthermore, acupuncture treatment has also produced positive results for the relief of morning sickness in early pregnancy<sup>19</sup>, breech presentation<sup>20</sup>, menopausal problems<sup>21</sup>, and headaches<sup>22</sup>. Moxibustion has been shown to be effective for the treatment of rheumatoid arthritis<sup>23</sup>, pain suppression<sup>24</sup>, and for the correction of breech presentation<sup>20</sup>. Thus, it appears that it would be incorrect to label TCM as “alternative” in the sense of alchemy and (modern) witchcraft. Given its history and scope, it is far less “alternative” than the art of medicine that is considered conventional in the West.

Even without the help of modern scientific equipment, ancient Chinese scholars discovered - through observation - many now-familiar aspects of biomedical science, such as the various effects of emotional stress on the immune system. Traditional acupuncturists are no less schooled than Western clinicians in their understanding of how the body functions, although to this day they use terminology that reflects Chinese medicine’s cultural and historic origins. In modern China, allopathic medicine and TCM are used side-by-side and TCM is now taught at Chinese universities. In addition, its results are reproducible under experimental conditions. As part of their medical school training, Chinese physicians must learn both medical systems, TCM and Western medicine. Today, TCM is practiced throughout China in allopathic hospitals, in traditional hospitals and in conjunction with allopathic medicine. Subsequently, hybrids of both forms of medicine have been developed.

Acupuncture is not only used by the Chinese. The Egyptians described their medical treatments in the Papyrus Ebers, 1550 BC, and referred to vessels that could correspond to the 12 main and a few minor meridians of acupuncture. Principles of acupuncture are also applied by the Inuit who live in our globe’s northern regions, the Bantu of South Africa, Arabs, and by a cannibalistic tribe in Brazil<sup>25</sup>. Broadening the scope of acupuncture outside China, Ben Kavoussi argues that Chinese natural philosophy and medicine have significant cognitive and epistemic similarities with certain esoteric health beliefs of pre-Christian Europe<sup>26</sup>. Following this line of argu-

ment, the non-decorative tattoos of the Stone Age mummies testify to the awareness of body locations suited to treat pain. These are now considered as acupuncture points, and it would seem therefore that a form of pain treatment, similar to TCM, was being practiced 5200 years ago in Central Europe<sup>27</sup>.

### The basic health concept in Traditional Chinese Medicine

Five fundamental principles form the primary concepts of TCM; these are listed in the text box below.

- ⑤ NATURAL LAWS GOVERN THE UNIVERSE.  
Humans are part of the universe and therefore exist according to and subject to those laws.
- ⑤ THE NATURAL ORDER OF THE UNIVERSE IS HARMONIOUS AND ORGANIZED.  
A life lived according to these laws will be harmonious.
- ⑤ THE UNIVERSE IS DYNAMIC; CHANGE IS A CONSTANT.  
Lack of change is contrary to the universe and therefore causes illness.
- ⑤ ALL LIFE IS INTERCONNECTED  
Onset of disease is described as an imbalance in homeostasis, reflected in changes in multiple pathways that are interconnected and interdependent
- ⑤ HUMANS ARE A PART OF THE UNIVERSE, AND INTIMATELY CONNECTED TO THE ENVIRONMENT AND THUS THE UNIVERSE.  
Health is affected by the environment.

### Salutogenesis

In accordance with these five fundamental principles, TCM endorses the principle of salutogenesis as the working mechanism of acupuncture. This is explained as follows. The human body is continually undergoing a process of injury, reaction and recovery. The healthy body is capable of responding to harmful influences with a curing process through which a new stability is achieved and the damage is repaired. This is called the self-healing mechanism, or: salutogenesis (salus= health; genesis= origin). Maintaining balance in building up and breaking down the body’s organism is vital for all life forms.

Common ‘damaging stimuli’ (= injuries) and subsequent recoveries are part of our life-system, and necessary for our physical development, the health of our immune system and human growth. This is important, too, for our course in life and our personal, emotional development and growth. Thus, TCM sees the human body as a system of dynamic interactions, rather than



an ensemble of anatomical units. Healthcare is then to be seen as a science of systems engineering, and therein differs from Western modern medicine. Modern medicine, notably in Cartesian thinking, stresses the accuracy and details of unit structures and unit functions within the human body<sup>1</sup>.

Chinese is a pictographic language. Chinese words are pictures, rather than sequences of letters. Similarly, Chinese thinking tends towards holistic processing of information and emphasizes the big picture over details<sup>29</sup>. Therefore, the Chinese discuss many issues simultaneously in an apparently haphazard order. In other words: “Nothing is settled until everything is”. This holistic thinking contrasts with the Westerner’s linear approach. For those rooted in the Western paradigm it is difficult, if not impossible, to understand the Eastern paradigm and vice versa – without causing tension between Western and Eastern scientific thinking.

To explain acupuncture, the TCM-teachers use metaphors, for instance the metaphor of the body as a landscape with a network of channels, rivers and waterways: the 14 (12+2) main meridians (with their 361 acupuncture points) are the channels. In the body, then, vital energy (Qi) circulates through a complex network of meridians just beneath the skin, but also within blood vessels. Each meridian corresponds to an organ or organ system<sup>30-31</sup>.

For a glossary of English and Chinese acupuncture terms used in this thesis, see Appendix 1. For some background reading on medical acupuncture, see Appendix 2

### Use of acupuncture in the Western world

Although acupuncture is a long-established system of healthcare, and is relied upon by millions of people in China and elsewhere in Asia, it is still relatively unexplored in the West. However, in spite of the dominant position of modern regulated Western medical practice throughout the world, the relationship between acupuncture and Western medicine is evolving. Increased use of complementary therapies is being reported in many areas of health care, particularly in those specialties in which conventional medicine can offer no complete cures.

<sup>1</sup> Descartes compared the human body to a machine, a healthy man to a well made clock: “All science is certain, evident knowledge. We reject all knowledge which is merely probable and judge that only those things should be believed which are perfectly known and about which there can be no doubts”, and “I do not recognize any difference between the machines made by craftsmen and various bodies that nature alone composes.” [28].

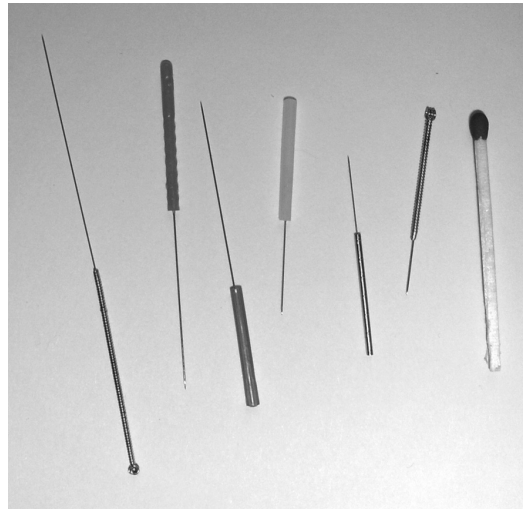
Acupuncture is characterized by its primary aim of restoring and promoting health, whereas in Western medicine the primary aim is eliminating disease. Although these aims can be reconciled, in practice the differences in attitude toward illness and healthcare are striking. For example, in ancient China, patients used to pay their TCM doctor as long as they remained healthy, seeing that only then they could earn the money to pay their doctor. In modern medicine, however, the doctor is paid for providing a cure in case of illness.

### Acupuncture in practice

The diagnostic methods for the TCM acupuncturist are: questioning, inspection and palpitation, percussion, listening and smelling. The objectives of the TCM practitioner are to understand both the essence of the patient and the nature of the disease. Only after reaching these understandings will the acupuncturist decide which points to treat, similarly to a GP making a choice among medical treatments.

There are several types of acupuncture treatment. The traditional form uses a combination of classical points, some of which may be farther down from or opposite to the affected area. The Chinese character for acupuncture point also means “hole”<sup>32</sup>, reflecting the idea that at such a point the needle can get entrance to deeper tissue layers. Another form of treatment involves the application of small and superficial needles encircling the symptomatic area (locus dolendi therapy, or: dry needling therapy)<sup>33</sup>. Inserting needles in points selected per treatment session from an array of classical points makes the treatment personalized and patient tailored.

Sometimes acupuncture points can be identified by anatomical markings such as eyebrows, hairlines or skin creases. Also, the distance between points is not measured by a standard method because body sizes differ. Instead, distances are measured by a metric called the “body inch”, which equals the distance between the distal joint (the knuckle nearest to the fingernail) and the middle joint of the middle finger of the patient. Apart from the described points, needles can be placed anywhere in areas of local tenderness (Chinese term; “ah-shi” point), penetrating from a fraction of a centimeter to several centimeters, depending on the thickness of the flesh and muscle at a given location.

**Figure 3.** Acupuncture needles

The needles are extremely fine, so the insertion is almost painless. Modern acupuncture needles are made out of stainless steel and come in various lengths and gauges of width (figure 3). These needles are disposable and used only once. Sensations such as tingling, heaviness, soreness, and pressure may or should occur (“Qi”,<sup>34</sup>). Sensations may also occur around the acupuncture point, along the meridian of which the

point is part of, and even in areas far from the point of insertion. Simultaneously, the acupuncturist feels a ‘tug’ on the needle, described in ancient Chinese text books as “like fish biting on a fishing line”<sup>35</sup>. Langevin introduced the term “needle grasp” for this phenomenon<sup>36</sup>. Using the needle actions, movements, or warmth treatments on these points (moxibustion), the acupuncturist invites the patient to trigger the self-healing mechanism and to de-block or move the stagnation in life-energy, and thus restore the equilibrium between physical, emotional and spiritual aspects. Depending on the message the acupuncturist wants to transmit, the needle may be left untouched or manipulated manually, electrically or with moxibustion during the treatment session. Following acupuncture treatment, one normally feels immediately animated, or relaxed. However, some patients may only experience the sense of regeneration a few days later, or sometimes not at all.

Since each patient is unique, the duration and frequency of each treatment will vary. A session may last from 45 minutes to more than an hour<sup>37</sup>. Generally, after six to twelve sessions, or fewer in acute situations, there will be a response to the treatment: recovery of the main complaint or a more generalized sense of improvement, such as more restful sleep, less painful menstruation, or a better circulation.

Many factors may influence the outcome. Animal research has shown that the placebo effect or suggestibility is not the determining factor. Modern technology has made it possible to use electrical stimulation or laser without acupuncture needle stimulation<sup>38</sup>.

### **Towards an evidence base for acupuncture**

Evidence-based medicine aims to apply the best-available evidence together with the physician’s expertise and patient’s values to optimize decision making<sup>39-40</sup>. It seeks to assess the quality of evidence of the risks and benefits of treatments<sup>41-42</sup>. While some find traces of the origin of evidence-based medicine in ancient Greece, others trace its roots to TCM<sup>43 (2)</sup>.

The main questions when researching medical treatments are:

1. How does it work? (Basic science)
2. Can it be applied to humans? (Translational research)
3. Does it work under strictly-controlled conditions? (Efficacy studies)
4. How effective is it in actual practice? (Effectiveness research)
5. Is it efficient to use? (Cost-effectiveness and cost-efficiency research)

Providing an evidence-base for acupuncture means that we must connect the results of acupuncture treatment from bench (1) to bedside (2) and transform it to practice (3), the community (4), and ultimately, society (5). Only then can prior (dis-)belief lead to posterior belief and acceptance of its benefit (Bayesian thinking). All these steps are necessary to meet the biomedical ethics principle that ‘the authorized healing should be based on an improvement that is more than what happens in the placebo arm of a randomized controlled trial’. It is known that acupuncture outcomes are individualized and diverse. Therefore it is important to develop research methods that are consistent with the aims and philosophical basis of acupuncture, but also comply with the evidence-based medicine principles within the biomedical tradition<sup>44</sup>.

Not researched in this thesis, however, is the understanding of the placebo effect in TCM. Much has been written about verum (real) acupuncture, placebo (minimal or sham) acupuncture and the not yet understood placebo mechanisms<sup>45-51</sup>. TCM trials and Cochrane reviews often conclude that the value of verum acupuncture is unclear, and sometimes not different from

2 Taoism is the most influential root of Oriental Medicine. The Taoists main focus was on the observable and natural laws of the universe and the implications for human beings’ relationship to the universe. 2500 years (5000BC - 500BC) of observational studies form the background and philosophy of TCM.

placebo acupuncture<sup>52</sup>. However, please note that half of the FDA trials on medical therapies do not show superiority to placebo medication. Turner et al. showed that over 30% of RCT's studying the efficacy of antidepressants are unpublished<sup>53</sup>. Of those published, 94% demonstrate benefit whereas of all FDA trials, only 51% show positive findings.

### Physiological evidence

Modern acupuncture research, spanning some 50 years, has focused on finding physiological evidence for the effect of acupuncture in five distinct and different fields<sup>54</sup>:

- the endogenous opioid system;
- anti-inflammatory actions;
- neuro-imaging;
- connective tissue;
- electrical properties.

**Endogenous opioid system** studies, mostly done in animal studies during the period 1970-1980, focused on acupuncture analgesia. Pioneers were Bruce Pomeranz and Ji-Sheng Han. Most of these studies used electro acupuncture and measured behavioral pain thresholds. They listed the pathways of the drug antagonist, the immunoassays and the histology, and laid the foundation for basic science studies of acupuncture.

More than 17 converging lines of evidence emerge from the published studies. The following are the main conclusions:

- a) Many different opiate antagonists block acupuncture analgesia. Low frequency electro acupuncture seems to be associated with reduced presence of nerve growth factor (NGF) and brain-derived neurotrophic factor in the hippocampus and NGF in the striatum in mice, and therefore induces modifications in brain neurotrophins<sup>55</sup>. Adenosine levels in tissue near the needle insertion points were 24 times greater after treatment, and mice with normal adenosine function experienced a two-thirds drop in paw pain. In contrast, mice that were genetically engineered to have no adenosine function gained no benefit from the treatment.
- b) Rats deficient in endorphins show poor acupuncture analgesia;

- c) Endorphin levels rise in blood and cerebrospinal fluid during acupuncture analgesia;
- d) Acupuncture analgesia is enhanced by protecting endorphins from enzyme degradation;
- e) Acupuncture analgesia is transmitted to a second animal by cerebrospinal fluid transfer and this effect is blocked by naloxone;
- f) mRNA for proenkephalin rises in the brain and pituitary with acupuncture analgesia;
- g) Levels of c-fos gene protein are elevated in endorphin-related areas of the brain during acupuncture analgesia.

There are a few caveats of the endogenous opioid studies. First, you need quite a strong stimulus to reach the effect: using electro acupuncture 1-6 V, 0.2-3 mAmps, for 10-30 minutes; or using manual acupuncture with 0.3 mm needles (as opposed to the usual 0.16-0.2 mm needles). Also, the effects are short-lived and last at most a few days. Finally, the results are not always specific to acupuncture points or meridians. More information can be found on <http://www.acupunctureresearch.org>.

**Anti-inflammatory actions** of acupuncture are mediated via the reflexive central inhibition of the innate immune system. Both laboratory and clinical evidence point to the existence of a negative feedback loop between the autonomic nervous system and the innate immunity. There is also experimental evidence that the electrical stimulation of the vagus nerve inhibits macrophage activation as well as the production of TNF, IL-1beta, IL-6, IL-18, and other proinflammatory cytokines. The use of acupuncture as an adjunct therapy to conventional medical treatment for a number of chronic inflammatory and autoimmune diseases seems plausible and should be validated by confirming its cholinergic<sup>3, 23, 56-57</sup>.

**Neuroimaging research** is the latest area of acupuncture research, logically following the endogenous opioid area. Neuroimaging studies have mostly focused on the noninvasive functional magnetic resonance imaging (fMRI) technique, some on PET, or MEG/EEG. Converging evidence from fMRI studies has demonstrated that acupuncture stimulation can modulate neural activities in a wide cortico-subcortical network, particularly the limbic system, the brainstem, and the cerebellum.

Hui and colleagues published a very interesting finding: acupuncture was associated with a decrease in the fMRI-BOLD signals, whereas these signals increased when subjects received a sharp pain stimulus. The authors interpret this finding as a pain-reducing effect of acupuncture through deactivation of a limbic-paralimbic- neocortical network as well as activation of somatosensory brain regions<sup>58</sup>. The amygdala, located in the medial temporal lobe as part of the limbic system, plays a dominant role in the affective encoding<sup>59</sup>. Acupuncture-related modulation of activity in the amygdala may contribute to stress reduction<sup>60</sup>. The results of different studies strongly suggest that acupuncture may mobilize these intrinsically organized dynamic functional systems to mediate its diverse effects<sup>61-63</sup>.

There are caveats: most of the stimuli used in de fMRI studies relied on the 'de-Qi' sensation and / or electro acupuncture, and studies were predominantly conducted with healthy individuals<sup>64</sup>. Nevertheless, chronic pain and other pain conditions are now being studied with the use of fMRI as well. Furthermore, it is unclear how long effects may last; and effects may overlap with a placebo effect<sup>65</sup>. However, Kong and colleagues showed that (placebo) acupuncture and analgesia may be configured through multiple brain pathways and mechanisms, although verum acupuncture produced greater fMRI signal decrease in pain-related brain regions during the application of calibrated heat pain stimuli<sup>48, 66</sup>.

The interaction between expectancy and acupuncture analgesia is under investigation. Positive expectations will amplify acupuncture analgesia, documented by sensory ratings and fMRI. In subjects with a high expectancy of relief, the clinical ratings of pain relief were similar for placebo acupuncture and verum acupuncture, although fMRI changes were greater in verum acupuncture. Placebo expectancy can be considered to induce a top-down effect, modulating the pain in the brain. Acupuncture, however, can be considered to induce a bottom-up effect, based on Tjen and Longhurst's finding that long-term EA-related inhibition of sympathoexcitatory cardiovascular responses induced opioids and GABA in the rostral ventrolateral medulla, but not nociceptin<sup>48, 67</sup>. Napadow and colleagues showed an effect of acupuncture on the cortical plasticity of the brain in patients with the carpal tunnel syndrome, suggesting that chronic pain patients respond to acupuncture differently than healthy controls, through a coordinated limbic network including the hypothalamus and amygdala<sup>68</sup>.

**Connective tissue** studies have been largely pioneered by Helene Langevin. The research areas are the anatomical, mechanical, and biochemical effects of needling and facial stretch on loose subcutaneous connective tissue and the extracellular matrix<sup>36</sup>. Extracellular matrix cells cause re-growth and healing of tissue. In human fetuses, for example, the extracellular matrix works with stem cells to grow and re-grow all parts of the human body, and fetuses can re-grow anything that gets damaged in the womb. It was long believed that the matrix stops functioning after full development, but its function as a device for tissue regeneration in humans in terms of injury repair and tissue engineering is being further researched (repair or replacement of portions of or whole tissues, i.e., bone, cartilage, blood vessels, bladder, skin etc.).

Several authors have suggested that acupuncture meridians may correspond with connective tissue<sup>69-70</sup>. Langevin and colleagues used ultrasound imaging and gross anatomical sections to locate the meridians in the human arm, and then by palpation of the 'holes' identified the acupuncture points on these meridians. According to Langevin, acupuncture meridians are often located in-between muscles, coinciding with the points where two connective tissue planes come together. Her previous research has shown that more pullout force is required to remove the needle from these points. More than 80% of acupuncture points were found to be located on connective tissue planes, three of the six meridians were on fascial planes between muscles, and two of the meridians were located on intramuscular fascial planes<sup>71</sup>.

Histological studies showed the working of the "needle grasp" in connective tissue<sup>36, 72</sup>. Inserting the acupuncture needle causes water movements in the extracellular matrix. The tension of the connective tissue decreases after stretching of the extracellular matrix. This phenomenon demonstrates that needle manipulation in acupuncture treatment activates (bidirectionally) the connective tissue. Furthermore, tissue stretch is believed to mediate inflammation<sup>50</sup>.

There are some caveats regarding connective tissue studies as well: Both the physiologic and clinical significance are as yet unclear; most studies were performed in healthy subjects or animal models; the duration of the effect is unknown and the distance of the effect is unclear. These basic science studies are nevertheless promising.

**Electrical properties** were reviewed by Andrew Ahn and colleagues<sup>73</sup>. The underlying hypothesis is that the acupuncture points are located where the skin resistance is low, and this low resistance may follow the meridian routes. Becker provided electrical conductivity maps of the skin at specific acupuncture points<sup>74</sup>. Studies about acupuncture points were poor in quality and yielded discrepant results, with insufficient evidence to draw conclusions. There is some evidence for a large spatial variability in skin resistance and the existence of low resistance points with a diameter of 1-4 mm. The question is if those low resistance points are actual acupuncture points?

Studies about the meridians were generally higher in quality. Seven of the nine studies showed positive associations between acupuncture meridians and lower electrical impedance and higher capacitance, but the evidence from these studies is unfortunately insufficient to draw conclusions. Besides, most studies concerned healthy subjects, in whom the resistance of the meridians most likely was not a reflection of an imbalance in health. Interestingly, Ahn and colleagues obtained positive results of electrodermal stimulation of specified acupuncture points (Jing points) in subjects with chronic pelvic pain<sup>75</sup>, although a preferential flow of charge along the meridian was reported. Further research and confirmation is needed.

The caveats of electrical properties studies are many: there are multiple confounders to the electrical measurements, the studies done so far are of poor quality, the physiological and clinical significance is unclear, and so is the duration of the effect of the treatment.

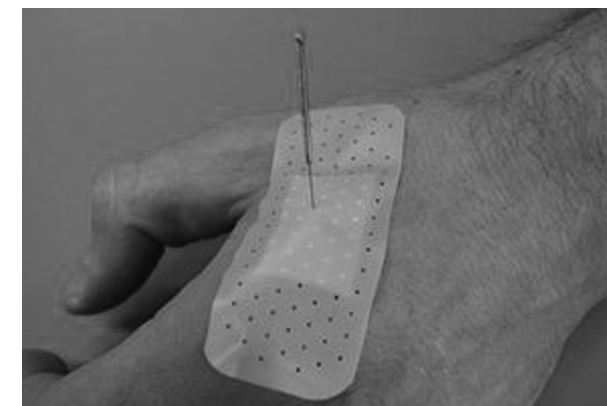
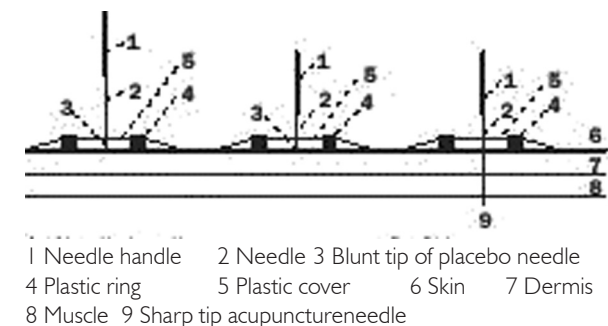
All-in-all, the peer-reviewed literature on the physiological effects of acupuncture shows multiple findings pointing towards a real and multi-dimensional effect, suggesting that scientific claims made by acupuncturists are valid.

### Blinding in acupuncture

Evidence-based medicine practitioners prefer blinded randomized controlled trials (RCTs) whenever possible. RCTs are high on the hierarchy of evidence, and only a meta-analysis of several well-designed RCTs is considered reliable evidence in modern Western medicine. Blinding of patients and researchers is advocated when designing RCTs, although not always possible. For example, it is practically impossible to blind a patient to the fact whether or not they have undergone coronary artery bypass surgery, and similar problems exist in TCM-research.

A control treatment in acupuncture research must be credible, regardless of whether the needling (placebo or verum) is performed by a single therapist or by several therapists. The fact that there has been no proven placebo for acupuncture has been a problem and has often confounded research findings. Apart from that, to successfully use blinding in acupuncture efficacy studies using the placebo needle (using minimal acupuncture or the non-penetrating needle<sup>76</sup>) (Figure 4), it is recommended that a strictly standardized needling procedure is used to minimize differences between therapists<sup>77</sup>. Furthermore, in some (Eastern) cultures it will be hard to find people who are not familiar with acupuncture and with the needling sensation who could participate naïvely in controlled acupuncture studies. Inevitably, as in all controlled studies, wishful thinking may influence the results. A solution could be to conduct unblinded pragmatic studies<sup>78</sup>, which are easier to interpret and reflect

**Figure 4.** The Streitberger (placebo) needle



The Streitberger needle<sup>76</sup>

treatment effects in a study population similar to real world practice, that is, patients are cognizant of the treatment received. Pragmatic studies demonstrate effectiveness in practice and include placebo effects. This is no different than what happens in studies evaluating surgery.



## Translational research in Traditional Chinese Medicine

Translational research is a way of thinking about and conducting scientific research to make the results applicable to the population under study. In medicine this implies translating findings from basic research quickly and efficiently into medical practice and, thus, into meaningful health outcomes – physical, mental, or societal outcomes. It seeks to move “from bench to bedside” (Table I). An important element of quality healthcare, and es-

**Table I.** Providing evidence-base for acupuncture.

Providing an evidence-base for acupuncture means we must connect the results of acupuncture treatment from bench (1) to bedside (2) and transform it to practice (3) and the community (4).

	Bench	Bedside	Practice	Community
Area	Basic Science >fundamental research	Medical diagnosis and biomedical perceptions >clinical research Improve people's health Patient centered outcomes	Safety	Preventive medicine Economic evaluation
Studies	Animal studies Efficacy studies: (Randomized) Clinical trials	Efficacy studies: (Randomized) Clinical trials	Effectiveness research: Pragmatic trials	Cost effectiveness studies Cost-consequence studies***
Result in	Practitioners interpretation of change, and practitioners perspective	Individualized outcome tools, Questionnaires like SPOT-ACM* [44] or ChQoL**[80]	Check list Guidelines	Implementation in health care and public health

\* A set of patient-centered outcome tools for acupuncture and Chinese medicine: MYMOP, MCQ, W-BQ12, PEI, SF-6D, optional combined with a problem-specific questionnaire [44]

\*\* Chinese Quality of Life instrument: three domains with four or five facets. Physical Form domain (complexion, sleep, stamina, appetite and digestion, climate adjustment); Spirit domain (consciousness, thinking, spirit of eye, verbal expression); and Emotional domain (joy, anger, depressed mood, fear, worry)[80]

\*\*\* In cost-consequence studies, all the costs and outcomes are measured and presented out in a table, which may allow for a wider variety of outcomes and be more useful for decision-makers [79].

pecially in complementary healthcare, is that it be patient-centered with a focus on the patient, including his or her preferences, values, and beliefs. Therefore additional types of patient-centered measures were developed, including patient satisfaction, decision regret, patient preference, and health-related quality of life<sup>44, 79-80</sup>. Typically, translational research involves moving the findings made at the laboratory bench through the process of animal studies, animal testing and small-scale human trials in order to determine whether the new treatment deserves testing on a wider scale. Interestingly, translational research in acupuncture is initiated the other way around: from bedside to bench.

The diversity of TCM, with a proliferation of styles and schools of practice<sup>81</sup>, is problematic for researchers schooled in the Western tradition. Nevertheless, comparing known standard treatment effects and costs with those of acupuncture treatments may help researchers demonstrate evidence of comparative effectiveness and cost-efficiency. There is a pitfall, however, in that assessing the clinical effect of acupuncture in state-of-the-art placebo-controlled randomized clinical trials is based on the assumption that distinct well-defined reproducible parts of acupuncture treatment exist, whereas in reality acupuncture consists of a multi-dimensional treatment with several interacting components<sup>82</sup>. This difficulty can be circumvented by utilizing pragmatic study designs<sup>10, 83-84</sup> to assess the whole treatment-system rather than evaluating the individual parts separately<sup>3</sup>. Although pragmatic studies give no answers about contextual factors inherent to the placebo effect<sup>85</sup>, they may be helpful to demonstrate comparative effectiveness and cost efficiency. According to internationally accepted thresholds for cost-effectiveness, acupuncture was found to be a cost-effective treatment strategy in patients with e.g. chronic neck pain<sup>86</sup>, low back pain<sup>9, 87-88</sup>, osteoarthritis<sup>89-90</sup>, headache<sup>91</sup>, allergic rhinitis<sup>92</sup>, dysmenorrhea<sup>93</sup>, and breech presentation<sup>94</sup>.

### Safety of acupuncture

Researchers summarized all acupuncture case reports published between 1966 and 1993, and found 395 instances of complications<sup>95</sup>. Many were minor, such as bruising or fainting, but 216 were serious, including several cases of pneumothorax and injury to the spinal cord. Only one death due to acupuncture was reported, caused by a needle penetrating the pericardium. Others reported the development of a Pott's puffy tumor after acupuncture

<sup>3</sup> In traditional acupuncture, the treatment effects are based on both specific and non-specific effects of treatment. Needling, moxibustion and cupping produce specific treatment effects whereas practitioner's enthusiasm and the process of making a diagnosis produce non-specific effects.

therapy<sup>96</sup>. In a large cohort, only 1 significant complication (pneumothorax) out of 7831 acupuncture treatment sessions was reported, representing 0.01% of patients<sup>97</sup>. White<sup>98</sup> reviewed significant adverse events associated with acupuncture in order to provide evidence on which to base efforts to improve the safety of acupuncture practice. He concluded that according to the evidence from 12 prospective studies which surveyed more than a million treatments, the risk of a serious adverse event with acupuncture is estimated to be 0.05 per 10,000 treatments, and 0.55 per 10,000 individual patients. This risk may be considered extremely low, below that of many common Western medical treatments. A meta-analysis of acupuncture for low back pain concluded that the range of adverse events reported is wide and that some events, specifically trauma and some episodes of infection, are likely to be avoidable<sup>8</sup>.

Commenting on the relative safety of acupuncture compared with modern Western treatments, the NIH consensus panel stated that “The incidence of adverse effects (of acupuncture) is substantially lower than that of many drugs or other accepted medical procedures used for the same condition. For example, musculoskeletal conditions, such as fibromyalgia, myofascial pain, and tennis elbow are conditions for which acupuncture may be beneficial, are often treated with, among other things, anti-inflammatory medications (aspirin, ibuprofen, etc.) or with steroid injections. The latter modern medical interventions have a known potential for deleterious side effects but are still widely used and are considered acceptable treatments.”<sup>99</sup>

### Scope and outline of this thesis

The mission of this thesis is to research and disseminate scientific inquiry into the traditional Chinese medicine system, which includes acupuncture and moxibustion. We hope that the reader will come to understand that TCM approaches can be evaluated by evidence-based methods of clinical research. With quantitative and qualitative research addressing clinical efficacy, cost-effectiveness and efficiency, physiological mechanisms, patterns of use and theoretical foundations, we tried to bridge the gap between Eastern and Western medical science and demonstrate the added value of acupuncture and moxibustion blended into today’s medicine in a Western country.

The thesis consists of three parts. Part one, the general approach, introduces the use of acupuncture in a general practice. The observational study (chapter 2) presents the health-related quality of life in patients with musculoskeletal complaints in a general acupuncture practice. Musculoskeletal complaints are associated with a large medical and societal burden. Although acupuncture is a frequently used therapy for musculoskeletal complaints, little is known about the effect on health-related quality of life (HRQoL). The aim of this pragmatic study was to gain insight into whether the HRQoL of patients undergoing routine acupuncture treatment for musculoskeletal complaints differs with that in a Dutch population sample; and to investigate changes in HRQoL during the course of acupuncture treatment.

In the second part we discuss also using TCM in the diagnosing of patients with complex regional pain syndrome type I (CRPS I). CRPS I can develop after severe trauma or surgery in the limbs. The estimated overall incidence rate of CRPS was 26.2 per 100,000 person years (95% CI: 23.0-29.7)<sup>100</sup>, and seventy-five percent of CRPS I patients are female. The etiology of CRPS I remains unclear, and there is no consensus on optimal management. Pain is the most common symptom in this disease, and other symptoms include allodynia, abnormal skin color and temperature change, hyperalgesia edema, abnormal sudomotor activity, tremor dystonia and trophic / motor disturbances<sup>101</sup>. One year after the initiating trauma, 22% of all patients report the combination of symptoms related to CRPS I, with substantial interference in daily life activities.

Chapter 3 gives a review of the literature about a number of inflammatory diseases, including CRPS I, in which acupuncture treatment was initiated as a complementary therapy or replacement for conventional pharmacological intervention. In addition, the anti-inflammatory action of acupuncture, mediated by neural immune reflexes, i.e. the cholinergic anti-inflammatory pathway of the central nervous system, is hypothesized.

The pilot study in chapter 4 reports a different TCM-approach to diagnose the patient with CRPS I, by questioning the menstrual cycle conform TCM, which might eventually lead to a new treatment approach: “diagnosis is not the end, but the beginning of practice” (citation, Martin H. Fischer).

The topic of the third part of the thesis is breech presentation. In breech presentation the baby enters the birth canal with the buttocks or feet first

as opposed to the normal head first presentation. This malposition of the fetus is noteworthy after 30 weeks of conception. No subjective symptoms are found in most cases, and it is only discovered by prenatal examination.

We describe, in chapter 5, the development and tracking of nonvertex position (mainly breech position) throughout pregnancy and the prognostic value of ultrasound in predicting nonvertex presentation at delivery in the Generation R study. We aimed to get better information about the natural history of the position of the fetus that leads to breech at delivery. In addition, we performed a systematic review and meta-analysis of the existing literature about (randomized) controlled trials on the acupuncture-type interventions on Zhiyin (BL 67) to elicit a version of a fetus in breech position in chapter 6, including a letter about the same topic.

In chapter 7 we report the results the modeling approach of a decision analysis and cost analysis of breech version by acumoxa offered to women with a breech fetus at 33 weeks of gestation. In this modeling approach, with sensitivity analysis we also considered the selective use of a) Moxa, b) the manipulation using external cephalic version, and c) home-births. As a result of the first two methods we found a greater opportunity for patients to consider home-births. Using the data of the pooled result of RCTs, Cochrane Database Systematic Review and data from the Dutch Perinatal Database, we found acumoxa effective and less costly than standard care in the Netherlands. With regard to this treatment it is interesting to note that it is the partner of the pregnant woman who provides the specific treatment to her: always on the same described acupoint, using the same temperature of the moxa. However, unlike the acupuncturist, the partner does not use the standard intake protocol of the non-specific treatment effects as practitioners' enthusiasm and the time consuming process of making a TCM diagnose.

Finally, in chapter 8, the main findings are summarized and discussed. Appendices have been added to help the reader gain a better understanding of the abbreviations, statistical and Chinese acupuncture terms used in this thesis (Appendix 1). Further nonprofessional background reading on Traditional Chinese Medicine can be found in Appendix 2.

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Chapter **2**

**Health-related quality of life in patients with musculoskeletal complaints in a general acupuncture practice: an observational study**

Ineke van den Berg  
Loek Tan  
I H van Brero  
K Tinka Tan  
A Cecile J W Janssens  
I M G Myriam Hunink

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## ABSTRACT

**Background** Musculoskeletal complaints are associated with a large medical and societal burden. Although acupuncture is a frequently used therapy for musculoskeletal complaints, little is known about the effect on health-related quality of life (HRQoL).

**Objectives** The aim of this study was to (i) compare the HRQoL of patients undergoing routine acupuncture treatment for musculoskeletal complaints with a Dutch population sample; (ii) investigate changes in HRQoL during the course of acupuncture treatment.

**Methods** An observational study of 26 patients between 18 and 65 years of age in a single acupuncture practice was performed. HRQoL was measured on eight functional domains using a RAND-36 health survey at baseline and after six and 12 treatment sessions. Baseline RAND-36 scores were compared to data from a Dutch population sample (n=1063) using t test, and longitudinal data were analysed using repeated measurement analyses.

**Results** At baseline, patients had significantly lower RAND-36 scores compared to the Dutch population sample for three domains: role-physical limitations (51.9 vs 79.4;  $p<0.001$ ), bodily pain (49.3 vs 79.5;  $p<0.001$ ) and social functioning (75.5 vs 86.9;  $p=0.005$ ). During the course of treatment, RAND-36 scores increased significantly for five domains: physical functioning (79.3 vs 97.4;  $p<0.001$ ), role-physical functioning (51.4 vs 94.1;  $p<0.001$ ), bodily pain (47.3 vs 95.7,  $p<0.001$ ), social functioning (74.5 vs 92.0,  $p<0.001$ ) and vitality (69.1 vs 85.7;  $p<0.001$ ).

**Conclusion** The observed improvements in HRQoL suggest a subjective, clinically relevant, benefit of routine acupuncture therapy in treating musculoskeletal complaints.

## INTRODUCTION

In Western countries, musculoskeletal complaints are an important cause of disability, morbidity<sup>1</sup>, absence from work<sup>2</sup> and increased healthcare costs<sup>3,4</sup>. In a large population-based study in The Netherlands, 75% reported having had musculoskeletal complaints during the past year and 44% reported chronic musculoskeletal pain<sup>1</sup>. About half of these people contacted a health professional for their symptoms, which indicates a large demand on healthcare services.

Although the number of patients using acupuncture in Western countries is growing<sup>5-7</sup>, and musculoskeletal complaints are common in acupuncture practice<sup>8</sup>, little is known about the outcome of acupuncture in a general acupuncture practice in treating musculoskeletal complaints and preventing its consequences. Several randomised controlled trials (RCTs) have demonstrated evidence for the reasonable efficacy of acupuncture in pain-relief and disease-specific outcomes for a variety of musculoskeletal conditions such as chronic lower back pain, chronic neck pain, knee and hip osteoarthritis<sup>9-13</sup>. RCTs generally only collect limited data, but for clinical relevance it is also important to know whether patients' lives improve.

Two German observational studies have demonstrated subjective beneficial effects of routine acupuncture practice for osteoarthritic pain and routine acupuncture practice by showing clinically relevant improvements in health-related quality of life (HRQoL) over time, that is, in general, patients are very satisfied, not only with the treatment, but also with the effects of the treatment<sup>8,14</sup>. These studies, however, offer limited information on the additional benefit of acupuncture for musculoskeletal complaints in other countries, because in Germany, a non-conventional therapy such as acupuncture is reimbursed by statutory sickness funds<sup>15</sup>.

The purpose of this study was to investigate in an observational study the effect of acupuncture on HRQoL in treating musculoskeletal complaints. We compared HRQoL profiles of patients seeking acupuncture treatment for musculoskeletal symptoms with HRQoL profiles of a Dutch population sample before and after treatment, and investigated changes in HRQoL during the course of acupuncture treatment. We expected a lower HRQoL prior to the treatment compared to the general population and an effect of acupuncture on HRQoL, but we had no prior hypotheses about the magnitudes of the effects.

## METHODS

### Patients

This observational study was performed in the Northwestern region of The Netherlands, between September 2002 and September 2003. Patients in this study visited the routine acupuncture clinic (<http://www.acupunctuur-vanbrero.nl/>) on their own initiative. All consecutive patients (age 18-65 years), who had musculoskeletal complaints eligible for acupuncture treatment, had no previous experience of acupuncture and gave written informed consent, were included. Excluded were pregnant or breastfeeding women, patients suffering from a terminal disease, patients receiving any other form of treatment for their complaints besides self-medication and patients participating in another clinical study. Patients were diagnosed and treated by the licensed acupuncturist (HvB) according to a Dutch social insurance classification system<sup>16</sup> which is based on the 10th edition of the International statistical classification of diseases and related health problems (ICD-10) from the World Health Organization<sup>17</sup>. Data were collected according to guidelines for registration of personal data.

### Controls

Data from a community survey were used to compare the health status of the study-population. The controls (1063 persons, age range 18-89) were randomly selected from the population register of a comparable area as the treated group and were participants of this population-based Dutch RAND-36 validation study<sup>18</sup>.

### Intervention

A licensed acupuncturist, with over 30 years of working experience, performed all acupuncture treatments. All participants were treated according to the principles of traditional Chinese medicine (TCM), meaning that the treatment frequencies as well as the number of needles and the used acupuncture points were determined individually for each patient and were adjusted to the patients' TCM profile during the course of therapy. On average, eight needles were used with a range of two to 12 needles per session. The treatment end point was 12 individualised sessions.

### Outcome measurement

HRQoL was measured using a validated Dutch language version of the RAND-36-item health survey 1.0 (RAND-36) which was adapted from the standardised short form (SF)-36 health survey<sup>18,19</sup>. Physical and mental health summery scores were derived from the eight RAND-36 scales: physical functioning, role functioning limitations due to poor physical health, bodily pain, general health, vitality, social functioning, role functioning limitations due to mental and poor emotional health. The SF-36 is designed for use in populations, not for drawing conclusions about HRQoL status at the individual level, as MYMOP and NHQ are<sup>20,21</sup>. HRQoL was measured before the start of the first acupuncture treatment (baseline measurement) and immediately after six and 12 treatment sessions. Additionally, patients were asked for the duration of their symptoms on the basis of which they were categorised into either acute (symptoms present <3 months) or chronic (symptoms present >3 months) patients. The Medical Ethics Committee Erasmus MC gave a declaration of no objection for publication (MEC-2009-422).

### Statistics

Scores for each scale of the RAND-36 were computed from the raw data according to the Dutch language version RAND-36 guidelines<sup>18</sup>. For each scale, responses to the corresponding survey-items were summed and converted to a 0-100 scale, in which 100 indicates the best possible functioning. Differences in age and sex distribution between the study sample and the general population sample were tested using t test and  $\chi^2$  test. Mean baseline RAND-36 scores were compared with the Dutch population, and compared between patients with acute and chronic symptoms using t tests<sup>18</sup>. To evaluate the clinical relevance of the mean RAND-36 changes, differences of >5 points were considered as clinically relevant<sup>17</sup>. To assess the course of HRQoL over time, the longitudinal data were analysed using a mixed model analysis for repeated measurements<sup>22</sup>. With this procedure, the contribution of the within-subject variation was taken into account and participants with incomplete follow-up data were included in the analysis. We examined the overall course over time for each scale by comparing estimated means using a mixed model analysis with the number of treatment sessions (0, 6 and 12), age and sex as covariates. The estimated means at treatment 12 were compared to the Dutch population sample and tested using t tests<sup>18</sup>.

We also explored differences in HRQoL between acute and chronic patients at baseline by comparing the mean RAND-36 baseline scores using t tests. We additionally performed an exploratory analysis of differences in HRQoL changes over time between chronic and acute patients by adding duration of symptoms and the interaction effect of duration of symptoms treatment in the repeated measurements analysis. Bonferroni correction was used to adjust for testing all eight scales of the RAND-36, resulting in the use of a significance level of  $p < 0.006$  ( $0.05/8$ ) for all tests we performed<sup>23,24</sup>. t Tests and  $\chi^2$  tests were performed using SPSS V.11 and longitudinal analyses were performed using the SAS Proc Mixed procedure in SAS V.9.13.

## RESULTS

### Characteristics of the study population

In total, 26 patients who met the inclusion criteria agreed to participate in the study. All completed the first and second assessments and 23 patients (88.5%) completed the third assessment. No adverse events were reported. Seventeen patients (65%) received treatment for chronic symptoms and nine (35%) for acute symptoms. Table 1 shows that 58% of participants were women, and mean age of 42.6 years (range 22-62), which was not significantly different from the Dutch population sample (65% women, mean age 44.1 years, range 18-89). The mean treatment period was 6.9 weeks between baseline and the sixth treatment session and 8.4 weeks between the sixth and the 12th treatment session (table 1). Treatment consisted of 12 sessions with an average duration of 30 min, administered over an average period of 14 weeks.

### Health-related quality of life

At baseline, the total study sample had significantly lower scores on the RAND-36 scales role-physical functioning (51.9 vs 79.4;  $p < 0.001$ ), bodily pain (49.3 vs 79.5;  $p < 0.001$ ) and social functioning (75.5 vs 86.9;  $p = 0.005$ ) compared to the Dutch population sample (figure 1 and table 2). No significant differences between both populations were found for the other RAND-36 scales. Five out of eight RAND-36 scales showed significantly higher scores after treatment compared to baseline (table 2) physical functioning, role-physical

functioning, bodily pain, social functioning and vitality. The mean RAND-36 scores after treatment were higher than the Dutch population sample scores for all eight RAND-36 scales (figure 2). The difference was statistically significant for the physical functioning ( $p < 0.001$ ), bodily pain ( $p < 0.001$ ), general health ( $p < 0.001$ ) and mental health scores ( $p = 0.001$ )

### Acute versus chronic patients

Baseline RAND-36 scores for acute patients were 15 points lower for bodily pain on role-physical functioning scores compared to chronic patients, but differences between acute and chronic patients were only statistically significant for the differences in bodily pain scores ( $p < 0.05$ ). The improvement in the five out of eight RAND-36 scales reported in table 2 was observed in both acute and chronic patients.

## DISCUSSION

We compared HRQoL of patients undergoing routine acupuncture treatment for musculoskeletal complaints to the normal population and described the perceived changes in physical and mental health during the course of acupuncture treatment. Patients with musculoskeletal complaints had lower RAND-36 scores on role-physical functioning, bodily pain and social-functioning at baseline, significantly improved HRQoL during treatment on five out of eight scales and had higher RAND-36 scores at follow-up on all scales compared to controls.

Before discussing our results, two important methodological issues need to be addressed. First of all, it is important to keep in mind that the design of this study does not permit any causal inferences concerning the effect of acupuncture itself, since no control group of patients was evaluated longitudinally to assess the impact of possible placebo effects, as patients went to the acupuncture clinic on their own initiative, likely with a prior open view regarding the effectiveness of acupuncture.

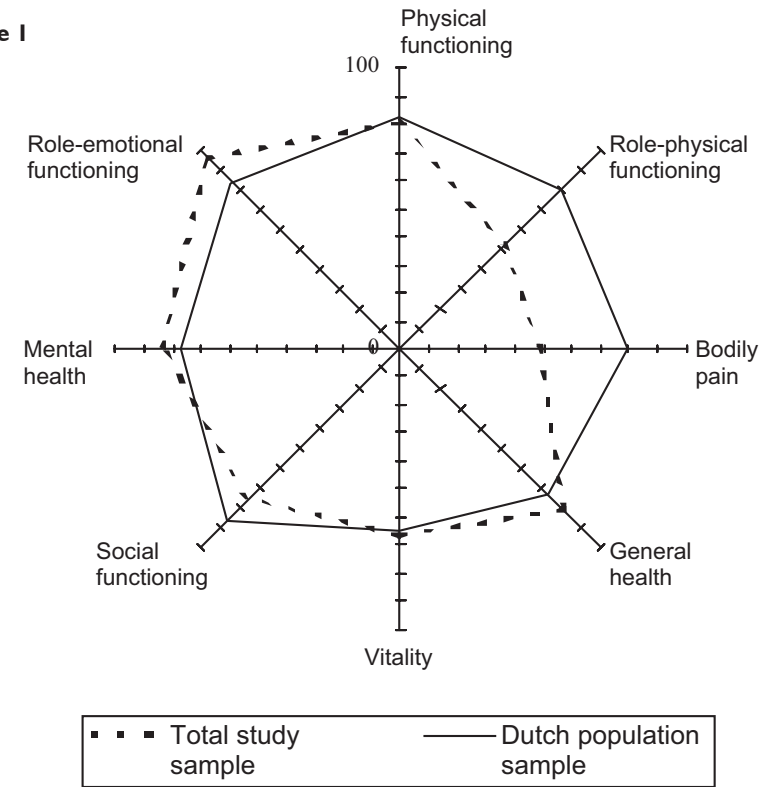
Second, the small number of patients provided us with insufficient statistical power to incorporate possible confounding factors in our model or compare the age and sex distribution between groups in more detail. Also, we had limited statistical power for the exploratory analyses of differences between



**Table 1** Characteristics of the study population

	<b>Total study sample (n=26)</b>	<b>Acute symptoms subgroup (n=9)</b>	<b>Chronic symptoms subgroup (n=17)</b>	<b>Dutch population Sample (n=1063)</b>
Sex (% women)	58	78	47	65
Age (mean, SD)	43 (10.6)	44 (10.3)	42 (11)	44
Diagnosis (n)		Aspecific lower back pain (3) Ischialgia (2) Epicondylitis lateralis (2) Osteoarthritis (1) Neck pain (1)	Aspecific lower back pain (2) Ischialgia (1) Epicondylitis lateralis (2) Osteoarthritis (1) Neck pain (3) RSI (3) Pain in upper extremity (2) Chronic headache (2) Other musculoskeletal complaints (1)	
Duration treatment period		Mean 7 weeks 9 weeks	Mean 7 weeks 8 weeks	
Treatment 0-6	7 weeks			
Treatment 6-12	8 weeks			

**Figure 1**



**Figure 1** Health-related quality of life scores of the total study sample and the Dutch population sample. Depicted values are mean scores of RAND-36 scales at baseline. The centre of the graph represents the lowest score possible for each scale. At a significance level of  $p < 0.006$  ( $p$  value adjusted using Bonferroni correction), significant differences between the total study sample and the Dutch population sample were found for RAND-36 role-physical functioning ( $p < 0.001$ ), bodily pain ( $p < 0.001$ ) and social functioning ( $p < 0.001$ ) scales.

acute and chronic patients and for other clinically interesting comparisons. While the statistical power increased by using the repeated measurement procedure with three measurements per patient, still the possibilities for subgroup analyses were limited.

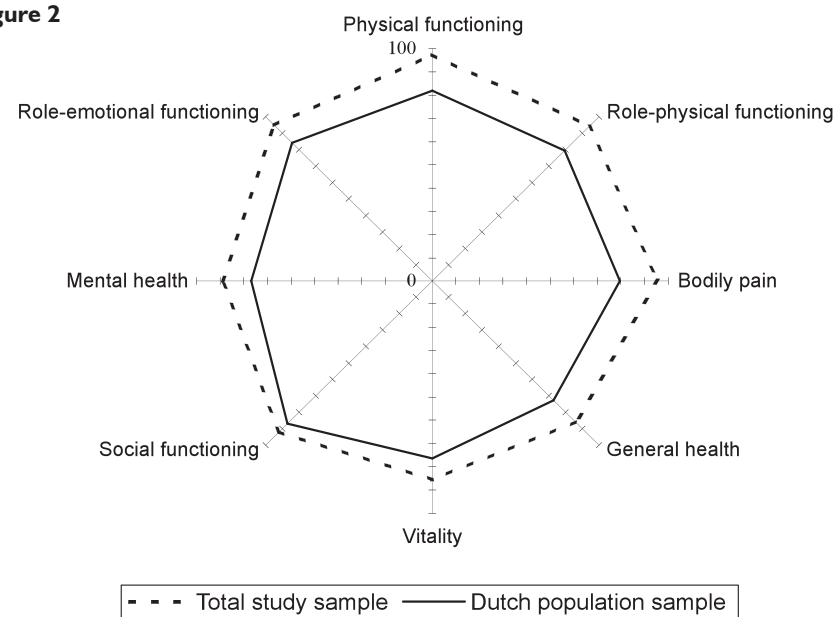
Our study demonstrated that the HRQoL of patients seeking acupuncture treatment for musculoskeletal symptoms differed significantly from the normal population. At baseline, HRQoL of both acute and chronic patients was lower on the RAND-36 role-physical functioning, bodily pain and social functioning scales compared to the Dutch population sample. The difference was most prominent for the physical health dimensions (role-physical



functioning and bodily pain). These findings are similar to results from a previous study in patients suffering from musculoskeletal pain who did not visit an acupuncturist for their symptoms<sup>25</sup>, suggesting that patients who seek acupuncture treatment are not a subgroup with particular HRQoL profiles, neither physically nor mentally.

The longitudinal findings of this study showed that the HRQoL of patients seeking routine acupuncture improved significantly during the course of treatment. This improvement in physical and mental health during the course of acupuncture treatment concerned the dimensions physical functioning, role-physical functioning, bodily pain, social functioning and vitality. The observed improvements were most pronounced in the course of the first six treatments for both acute and chronic patients. Although it is unusual that both acute and chronic patients require the same number

**Figure 2**



Health-related quality of life scores of the Dutch population sample and the total study sample at the end of treatment. Depicted values are mean scores of RAND-36 scales at the end of the treatment period. The centre of the graph represents the lowest score possible for each scale. At a significance level of  $p < 0.006$  ( $p$  value adjusted using Bonferroni correction), significant differences between the total study sample and the Dutch population sample were found for RAND-36 scales physical functioning ( $p < 0.001$ ), bodily pain ( $p < 0.001$ ) general health ( $p < 0.001$ ) and mental health ( $p = 0.001$ ).

**Table 2** Health-related quality of life in a general acupuncture practice at baseline and after 6 and 12 treatments

RAND-36 scales	Baseline (se)	After 6 treatments (se)	After 12 treatments (se)
Physical health			
Physical functioning	79 (2.3)	93 (1.5)	97 (0.9)
Role-physical functioning	51 (6.8)	81 (5.6)	94 (5.3)
Bodily pain	47 (4.3)	84 (2.9)	96 (1.7)
General health	83 (3.7)	85 (4.0)	86 (3.5)
Mental health			
Vitality	69 (4.9)	81 (3.9)	86 (4.3)
Social functioning	75 (4.9)	91 (4.3)	92 (4.6)
Mental health	84 (2.9)	87 (3.2)	89 (3.7)
Role-emotional functioning	96 (4.2)	97 (4.3)	95 (4.9)

Values are mean RAND-36 scores, as estimated by SAS Proc Mixed analyses, with standard errors.

of treatments, the researcher chose this fixed number in both groups for statistical reasons to deal with the small number of patients in the treatment group. For all RAND-36 scales, the observed improvement was larger than the five points considered clinically relevant<sup>17</sup>.

The most distinct improvements were observed with regard to the scales role-physical functioning, bodily pain and social functioning, indicating that the largest improvements were symptom-related. Importantly, for these RAND-36 scales--in which a lower score compared to the Dutch population sample was found at baseline-- the scores after treatment were higher than the scores of the Dutch population sample. In the Dutch population sample the age was older and therefore might reduce their HRQoL scores. However, given that the mean age is the same and that the very old are only a small part of the total sample, we think it is unlikely that the differences are only explained by an effect of age. Considering the normal baseline results compared to the population sample, the observed improvements with regard to the RAND-36 scale physical functioning was significantly higher than the mean score of the Dutch population sample. It should be noted that the better health on all scales compared to the general population may be due to response shift, which is defined as an adaptation to changing health,

a beneficial mental process that can help in adapting to a new situation<sup>26</sup>. Response shift is more likely to occur when the disease experience is new, intense or pervasive<sup>27</sup>. Two-thirds of our population had long lasting musculoskeletal complaints, who may no longer expect improvement of their symptoms. All the patients were treated by the same acupuncturist what might affect the generalisability of our findings.

The understanding of the holistic model of acupuncture treatment embedded in Chinese medicine is limited by a lack of inquiry into the dynamics of the process where “the whole is greater than the sum of the parts”<sup>28-31</sup>. Paterson and Britten<sup>32</sup> found that treatment effects were perceived as changes in symptoms, changes in energy and changes in personal and social identity. After treatment, the study population had a significantly higher score on the RAND-36 scales for general health and mental health as compared to the general population. The longitudinal results of this study suggests that patients experience acupuncture as relevant for their recuperation, also supported by the fact that the majority of the study population completed the full course of 12 treatment sessions, even though acupuncture is often only partially reimbursed after prescription and often leads to private expenses. Our findings support the view that acupuncture therapy has beneficial effects in patients with musculoskeletal complaints. This is in concordance with the findings of two previously mentioned observational studies that reported beneficial effects of acupuncture on HRQoL<sup>8,14</sup> and with a variety of RCTs on the efficacy of acupuncture in treating musculoskeletal complaints<sup>9,10,12,13,33,34</sup>. In order to obtain a more accurate and robust evidence for the role of acupuncture in daily practice with regard to musculoskeletal complaints and its consequences, more extensive randomised controlled research is needed. For instance, we suggest conducting a large controlled study on the usefulness of acupuncture across multiple acupuncture practices and for specific musculoskeletal complaints. Also, the characteristics of patients that seek acupuncture treatment for musculoskeletal complaints need to be addressed in detail. Furthermore, it seems necessary to assess whether the apparent benefit patients obtain from acupuncture treatment also translates to less disability, morbidity and absence from work and healthcare expenses in the long term.

In conclusion, this study demonstrated that patients who sought acupuncture treatment for musculoskeletal complaints in an out-patient acupuncture clinic showed a lower HRQoL at baseline, mainly with respect to physical

domains. During the course of acupuncture treatments, patients experienced significant, clinically relevant improvement in HRQoL. Therefore, acupuncture should be considered as treatment option for patients with musculoskeletal complaints in general practice.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Medical Ethics Committee Erasmus MC who gave a declaration of no objection for publication (MEC2009-422).

Provenance and peer review Not commissioned; externally peer reviewed.

## SUMMARY POINTS

- Standard assessments of quality of life include eight dimensions
- Twenty six patients with musculoskeletal disorders showed significant deficits in three dimensions
- Five dimensions showed improvement after a course of acupuncture

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Chapter **3**

**Anti-inflammatory actions  
of acupuncture, a review  
of the literature**

Freek J. Zijlstra  
Ineke van den Berg  
Frank J.P.M. Huygen  
Jan Klein

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## ABSTRACT

Acupuncture has a beneficial effect when treating many diseases and painful conditions, and therefore is thought to be useful as a complementary therapy or to replace generally accepted pharmacological intervention. The attributive effect of acupuncture has been investigated in inflammatory diseases, including asthma, rhinitis, inflammatory bowel disease, rheumatoid arthritis, epicondylitis, complex regional pain syndrome type I and vasculitis.

Large randomised trials demonstrating the immediate and sustained effect of acupuncture are missing. Mechanisms underlying the ascribed immunosuppressive actions of acupuncture are reviewed in this communication.

The acupuncture-controlled release of neuropeptides from nerve endings and subsequent vasodilative and anti-inflammatory effects through calcitonin gene-related peptide is hypothesised. The complex interactions with substance P, the analgesic contribution of  $\beta$ -endorphin and the balance between cell-specific pro-inflammatory and anti-inflammatory cytokines tumour necrosis factor- $\alpha$  and interleukin 10 are discussed.

## INTRODUCTION

In China, acupuncture has been used in the treatment of several diseases for at least 5200 years. In Europe and the USA, this integral part of traditional Chinese medicine has become a visible component of the health delivery system and has steadily claimed its usefulness in complementary medicine. Although sometimes without a clear objective beneficial effect, an increasing number of patients, especially those suffering from chronic diseases, are seeking acupuncture treatment and pursue (lay claims to) additional healthcare. Consequently, this increases costs, even though it does not always provide a clear objective beneficial effect<sup>1</sup>.

The widespread application of acupuncture includes the treatment of infections, inflammatory diseases like rheumatoid arthritis, autonomic dysfunction, neurological diseases like migraine, pain, cardiovascular diseases, pulmonary diseases like asthma, drug abuse, psychological disorders and many other illnesses<sup>2</sup>. Based on the effects seen in this variety of diseases, acupuncture could be divided into two main subjects: acupuncture analgesia and curative acupuncture. In general, analgesia is obtained by short-term acupuncture, whereas curative acupuncture requires long-term acupuncture treatment procedures.

Traditional Chinese acupuncture is characterised by a holistic approach to the management of the disease. The skill of the acupuncturist lies in the ability to work not only with a clear-cut diagnosis, but also takes into account the complex pattern of disease-related factors. The exact pattern and degree of disharmony is unique for each individual. Therefore, the practitioner of traditional acupuncture will approach each patient with a personalised treatment plan. This plan focuses on improving the overall well-being of the patient, rather than the isolated treatment of specific symptoms or disease. The basic health concept in traditional Chinese medicine consists of the body's vital energy (Qi), circulating unidirectionally through a complex network of channels (meridians) just beneath the skin, but also moving within blood vessels. It permeates organs and tissues, and is behind all physiological processes. Health is the harmonious, uninterrupted flow of Qi, and disease ensues when there is disruption of Qi flow. Factors that can affect Qi flow include emotional states such as anxiety, stress, anger, fear or grief, poor nutrition, weather conditions, hereditary factors, infections and trauma. By inserting needles, the acupuncturist tries to recover the equilibrium

(the equal and dynamic opposite qualities of Yin and Yang) between physical, emotional and spiritual aspects of the individual, and to improve energy flow and energy quality. Additional activation can be obtained through manipulation of the needle or electro-stimulation at different frequencies. The most common manifestations of Yin and Yang in diseases are excess and deficiency states. Health is defined as the balance of Yin and Yang<sup>3</sup>. Improvement of local blood circulation, distribution and bloodletting could be the main aspects of which acupuncture-derived effects in inflammatory diseases could be attributed<sup>4</sup>. In the case of inflammation, differential effects of acupuncture on acute and chronic stages of the disease could be considered, more or less expressed by clinical symptoms like burning pain, redness, swelling, changing temperature and loss of function.

Beyond these manifestations, inflammatory mediators could represent sub-sequential mechanisms that are involved, but could also represent disease activity. For example, in inflammatory bowel disease, the blood flow is increased and vascular resistance diminished<sup>5</sup>, whereas the release of different inflammatory mediators is time and region dependent and could be influenced by external factors<sup>6-8</sup>.

In acupuncture, the insertion of a needle induces marked changes close to the needle in all the different tissues that are penetrated. These peripheral events might improve tissue function through vasodilatation in the skin due to axon reflexes, which cause an immediate flare reaction<sup>9</sup>. This vasodilative effect could be caused by the release of calcitonin gene-related peptide (CGRP) upon stimulation of A $\delta$  or C fibres<sup>10,11</sup>. The local release of  $\beta$ -endorphin could be responsible for the short-term analgesic effect, whereas the neuropeptide-induced release of anti-inflammatory cytokines could be derived from lymphocytes and secondary activating cells, such as macrophages. In the periphery, the real level of CGRP is of crucial importance. Usually CGRP has been shown to be pro-inflammatory, but in low doses it has a potent anti-inflammatory action<sup>12</sup>. In this respect the release of another neuropeptide, substance P, is not likely to attribute to this phenomenon<sup>13</sup>, but could regulate CGRP release from nerve endings<sup>14</sup>. In the present review, a hypothesis is presented concerning the anti-inflammatory action of needle acupuncture through a dose'-related and time-related release of CGRP and a hypothesised preferential shift to the subsequent formation of anti-inflammatory cytokines.

### **Inflammatory diseases**

In the following, a number of inflammatory diseases will be reviewed in which acupuncture treatment was initiated as a complementary therapy or replacement for conventional pharmacological intervention. Then, the role of mediators of inflammation in acupuncture will be discussed and a proposed mechanism of action to use acupuncture will be hypothesised.

### **Asthma**

Numerous uncontrolled trials as well as a limited number of controlled trials have been published with contradictory and conflicting results after the short-term or long-term use of acupuncture in the treatment of asthma. In most studies, a relatively small number of patients were included, whereas methodological procedures were incompletely described. Various outcome parameters such as lung function, quality-of-life questionnaires and reduction of medication were used to reflect improvement of the disease.

The use of acupuncture to suppress the daily intake of orally given corticosteroids and inhaled  $\beta$ 2-adrenergic agonists was investigated<sup>15</sup>. In an open trial, patients with bronchial asthma were treated by acupuncture. This resulted in a good therapeutic effect (96% effective rate). Patients initially were treated in 15 consecutive sessions and received 10 follow-up treatments to consolidate the curative effect as marked by a decrease of corticosteroid intake and diminished use of aerosols. The investigator concluded that at least 30 sessions in 3 months should be offered to initiate this effect, followed by 10 more sessions per year to prevent a relapse. The extensive treatment with acupuncture could explain the lack of effect seen in other studies.

In a double-blind cross-over study, the effect of 2 weeks of acupuncture treatment on patients with stable asthma was investigated<sup>16</sup>. Although a significant improvement of the quality of life and a reduction of the usage of inhaled  $\beta$ 2-adrenergic agonists was observed, the respiratory function was not affected. This is in contrast with another placebocontrolled study in which patients with moderate persistent asthma, who were only treated with inhaled  $\beta$ 2-adrenergic agonists, received a treatment with acupuncture four times<sup>17</sup>. This relatively short course of treatment did not affect daily intake of inhaled  $\beta$ 2-adrenergic agonists. No changes in lung functions, bronchial hyper-reactivity or symptom scores were observed.

In a randomised, controlled study, both the additive effect of acupuncture to conventional therapy and the immune-modulating effects on patients with allergic asthma was monitored<sup>18</sup>. All patients were treated 12 times for 30 min over a period of 4 weeks. Subjective parameters like the patients' general wellbeing, and more objective parameters like biochemical measurements in blood, were determined before and after completion of the acupuncture treatment. General well-being significantly improved in the acupuncture group (79%) in comparison with the control group (47%). Furthermore, lymphocyte proliferation and CD3<sup>+</sup> and CD4<sup>+</sup> cells increased, whereas the number of eosinophils significantly decreased in the acupuncture group.

Single application of laser acupuncture performed in a double-blind, placebo-controlled, crossover study to investigate the protective effect on cold dry air hyperventilation-induced bronchoconstriction revealed no significant protection in paediatric and adolescent patients<sup>19</sup>. Forced expiratory volume and the expiratory flow were unaffected by single laser acupuncture.

In 1991, Kleijnen et al. published a systematic review of 13 controlled clinical trials pertaining to the use of acupuncture in the treatment of asthma during the period 1963 -1989<sup>20</sup>. Only three studies of acceptable quality resulted in favourable effects. Recently, other systemic reviews and meta-analyses of all randomised clinical trials in the published literature comparing acupuncture at real and placebo points in asthmatic patients were performed. The period 1970 - 2000 was evaluated by Martin et al<sup>21</sup>. Peak expiratory flow rate, forced expiratory volume and forced vital capacity were collected as objective outcome parameters. In this analysis, no significant overall effect of acupuncture to reduce asthma could be confirmed. After induction of broncho-constriction, however, a significant effect was observed. The authors concluded that this meta-analysis was limited due to shortcomings of the individual trials and a not clearly described use of placebo acupuncture. Others who reviewed the efficacy of acupuncture in asthma concluded that up to now evidence is lacking, also due to inadequately performed investigations<sup>22,23</sup>. In conclusion, mainly based on clinical outcome parameters, there is presently not enough evidence to make specific recommendations about the value of acupuncture in the treatment of asthma (Table 1).

**Table 1.** Summarised effects of acupuncture in inflammatory diseases

	<b>Effect</b>	<b>Ref.</b>
Asthma	+/-	15-20
Rhinitis	+	25-29
Ulcerative Colitis	+	32-34
Rheumatoid Arthritis	+/-	35-39
Epicondylitis	+	41-46
Complex Regional Pain Syndrome	+	49-52

(+) significant effect or (+/-) no clear disease related effect

### Rhinitis

Treatment by acupuncture is frequent among adults with asthma and rhinosinusitis, and therefore should be taken into account by health-care providers<sup>1,24</sup>. In acute sinusitis, acupuncture resulted in an improvement in children with chronic and recurring frontal sinusitis<sup>25</sup>. In the treatment of seasonal allergic rhinitis, acupuncture has been proven to be effective. In a small single-blind crossover study, acupuncture (three times a week during a 4-week period) improved subjective symptom scores, although a reduction in medication was not observed<sup>26</sup>. In allergen-provoked rhinitis acupuncture, acupuncture therapy was not effective when regarding the objective criteria, although again symptoms scores as registered in the diary of complaints revealed a reduction<sup>27</sup>. Desensitisation of allergic rhinitis using acupuncture endermic points of the head with the extract of positive allergens proved to be effective in an open study including 102 cases. After a follow-up of 2 years, a significant population (72%) showed a curative effect, mainly reflected by a reduced diameter of redness and reduced swelling of the skin<sup>28</sup>. In an open study, the positive effect of acupuncture on atrophic rhinitis was demonstrated. The improvement was documented by functional changes of the nasal mucosa (mucociliary transport, secreted volume and surface temperature)<sup>29</sup>.

### Inflammatory bowel disease

The use of alternative medicine in bowel diseases was already investigated almost two decades ago. Significantly more patients with irritable bowel syndrome (11%) appeared to consult practitioners of alternative medicine than patients with Crohn's disease (4%)<sup>30</sup>. Nowadays, traditional and com-



plementary therapies such as acupuncture are more frequently combined in the treatment, relief and control of Crohn's disease<sup>31</sup>. Until now, only limited data is available for the complementary use of acupuncture in ulcerative colitis with or without moxibustion<sup>32-34</sup>. These data, however, indicate that acupuncture could attribute to recovery in patients with active inflammatory bowel disease.

### Rheumatoid arthritis

In another autoimmune disease, rheumatoid arthritis, which sometimes also results in the development of Crohn's disease, successful treatment with acupuncture<sup>35</sup> and moxibustion has been reported<sup>36,37</sup>. Although the results clearly showed a beneficial effect in the reduction of symptomatic pain, the small sample size is a matter of concern. In other placebo-controlled cross-over studies, in a large number of patients with rheumatoid arthritis, acupuncture could not attribute to any improvement in general health, pain request or the examination of the number of swollen joints, nor to a diminished analgesic intake<sup>38,39</sup>. Until now, the usefulness of acupuncture as a complementary and alternative medical therapy in rheumatoid arthritis still has to be demonstrated in large randomised trials<sup>40</sup>.

### Epicondylitis

The clinical efficacy of acupuncture was also investigated in chronic lateral epicondylitis of the elbow (tennis elbow). The immediate analgesic effect of a single acupuncture stimulation in a placebo-controlled single-blind trial has been reported<sup>41</sup>. In a comparative study, both classical and superficial needle insertion was studied in a short-term treatment schedule stimulating five selected acupuncture points during 10 treatments in 3 weeks<sup>42</sup>. Classical acupuncture was only superior to superficial needle insertion after all treatments were applied, but not at 3-month and 1-year follow-ups. Laser treatment applied to the same acupuncture points, however, did not improve subjective and objective outcome parameters significantly in comparison with a placebo<sup>43</sup>. Psychosomatic factors could attribute significantly in the positive short-term effects of pain reduction<sup>44</sup>. As seen in the improvement of outcome parameters including pain scores, function, disability, strength and quality of life, short-term effects are promising<sup>45</sup> but acupuncture failed to stabilise the disease and did not contribute to further recovery<sup>46</sup>.

### Complex regional pain syndrome type I

Recently, we confirmed that complex regional pain syndrome type I (CRPS I), formerly indicated as posttraumatic sympathetic dystrophy or Sudeck's atrophy, developed in one or more extremities, and should also be considered as the result of an inflammatory reaction after neurogenic stimulation<sup>47,48</sup>. Two case reports<sup>49,50</sup> and two randomised trials predominantly focused on pain reduction<sup>51,52</sup> have published improvements after long-term acupuncture treatment. Other symptoms of inflammatory reactions including swelling, mobility, temperature and redness were also observed. In comparison with placebo-treated patients, no significant improvement of these parameters could be proven.

### Vascular diseases

Inflammation of the vascular system could attribute to some of the aforementioned inflammatory diseases. The promotion of blood circulation by acupuncture could positively affect the enrolment of the whole cascade of inflammatory mediators that are undoubtedly involved in the subsequent processes during chronic inflammation<sup>53,54</sup>. In the context of migraine, neurogenic inflammation could also play an important role<sup>55</sup>. Elevated plasma levels of CGRP during headache suggest that this initial inflammatory mediator is involved. In general, acupuncture has additional value in the treatment of primary headaches<sup>56,57</sup>.

**Table 2.** Inflammatory mediators reported in acupuncture

Neuropeptides	Substance P Neurokinin A Neuropeptide Y Vaso-active Intestinal Peptide Bradykinin Calcitonine Gene Related Peptide $\beta$ -Endorphin
Cytokines	IL-1 $\beta$ , IL-2, IL-4, IL-6, IL-10 IFN- $\gamma$ , TNF- $\alpha$
Other vaso-active substances	Nitric oxide Eicosanoids Serotonin



### Inflammatory mediators

In general, inflammation is associated with increasing temperature, oedema, redness, pain and loss of function. Furthermore, the direct and indirect effects of individual neuropeptides, cytokines and vasoactive mediators<sup>47</sup> could be considered to play an intermediate role during and after acupuncture has been assessed. Assuming local blood flow is indeed stimulated by acupuncture<sup>58,59</sup>, the neurogenic formation of vasoactive mediators could regulate blood flow and blood distribution to affected organs and tissue after inflammation has been initiated. Acupuncture activates the defence systems. It influences specific and non-specific cellular influx, activation of cell proliferation and regulation of subsequently involved cells that will result in a complex mechanism of transport, further breakdown and clearance of all bioactive mediators<sup>60</sup> (Table 2).

### Neuropeptides

Calcitonine gene-related peptide is a potent vasodilator<sup>10</sup> that has been shown to have a physiological and pathological role in neurogenic inflammation, migraine, thermal injury, circulatory shock, pregnancy and menopause, hypertension and heart failure, and has been proven to be cardioprotective<sup>61</sup>. Both substance P and CGRP have important roles in oedema formation and inflammation, and when transported centrally these neuropeptides can cause excitation<sup>62</sup>.

In patients with CRPS I, blood samples did not show an elevation of substance P and neurokinin A, whereas neuropeptide Y, CGRP, bradykinin and vasoactive intestinal peptide (VIP) were increased four-fold<sup>63</sup>. Intra-neural substance P contributes to the severity of inflammation<sup>64</sup>. After intra-arterial infusion in the human forearm, substance P provoked vasodilatation, flushing and plasma extravasation<sup>65</sup>. In musculocutaneous flaps in the rat, increased blood flow affected by acupuncture was comparable with the effects observed after injection of substance P and CGRP<sup>59</sup>. In rats, acupuncture induced the release of substance P from peripheral terminals of primary sensory neurons<sup>66</sup>. After repeated electro-acupuncture, significantly higher concentrations of substance P and other neuropeptides such as neurokinin A and neuropeptide Y were found in the rat brain<sup>67</sup>. The acute release of neuropeptides can be mimicked and easily provoked after application of capsaicin, the bioactive substance of red pepper. Acupuncture could diminish capsaicin-induced oedema in the rat paw, indicating a promi-

nent role for substance P and other neuropeptides<sup>68</sup>. In dogs, the concentrations of substance P were determined in the skin, muscle and subcutis of acupoints and control points, showing an increased release of substance P after acupuncture<sup>69</sup>. On the other hand, an observation in rabbit tooth pulp showed that, after an initial substance P release had already been evoked, electroacupuncture suppressed this release<sup>70</sup>. In humans, during labour, the content of substance P in serum declined after acupuncture had been applied<sup>71</sup>, but increased in patients suffering from fibromyalgia<sup>72</sup>. In both observations the analgesic effect of acupuncture was significant. In samples taken from the saliva of healthy subjects, the release of substance P was hardly affected after acupuncture, although neuropeptide Y and CGRP were markedly increased<sup>73</sup>.

Needling of acupuncture points could result in activation of afferent fibres of peripheral nerves, which induces the release of endogenous opiate peptides from nerve cells. Beta-endorphins are believed to play an important intermediate role in the regulation of the analgesic effects obtained through acupuncture<sup>74,75</sup>. Beta-endorphin concentrations in spinal fluid and plasma of horses, however, were not elevated after acupuncture<sup>76</sup>. Although prenatal acupuncture treatment in women significantly reduced the duration of labour, serum levels of  $\beta$ -endorphin were not influenced<sup>77</sup>. In another study, however 90 patients suffering from various painful disorders were subjected to acupuncture. Plasma bendorphin levels were increased considerably, resulting in an elevated immunologic response<sup>78</sup> reflected by lymphocyte markers CD3, CD4 and CD8. In curative (long-term) acupuncture, interactions between b-endorphins and cytokines could therefore result in an increased formation of anti-inflammatory cytokines<sup>79</sup> such as interleukin (IL)-10 and/or a diminished production of pro-inflammatory cytokines, possibly being the most prominent mechanism of action underlying the attributive effect of acupuncture in chronic inflammatory diseases. Very recently, the existence of regulatory IL-10-dependent T-cell populations was documented in allergic diseases<sup>80</sup>.

### Cytokines

Recently, the effect of acupuncture on regulation of cytokine production in asthma has been published<sup>81</sup>. Clinical signs of asthma improved markedly. In peripheral blood of asthmatic patients, the mean IL2 and IL-6 plasma levels were decreased, whereas interferon (IFN)- $\gamma$ , IL-4 and tumour necrosis

**Table 3.** Variables in acupuncture

Controlled studies	Non-treated controls Placebo needled acupuncture Placebo (non) invasive acupuncture Laser Superficial ('minimal') 'Wrong' acupoints Penetrating/invasive acupuncture Disease-related acupuncture Individualised acupuncture
Style	Chinese traditional acupuncture Japanese superficial acupuncture Western-oriented acupuncture
Treatment schedule	Single treatment Frequency Repeated treatments short term Repeated treatments long term Follow-up treatment
Needle	Point selection per session Number of acupoints used Number of needles inserted Depth of insertion, needle type Duration of needling
Stimulation	Manual Electrical
Blinding	Patient Acupuncturist Physiotherapist Assessor Statistician
Co-interventions	Moxibustion Herbs Physical therapy Pharmaceutical intervention

factor (TNF)- $\alpha$  were increased. After acupuncture IFN- $\gamma$ , IL2, IL-4 and IL-6 were elevated and TNF- $\alpha$  was reduced. In allergic rhinitis, plasma concentrations of IL-2, IL-6 and IL-10 were determined before and after acupuncture in comparison with healthy controls<sup>82</sup>. In all allergic rhinitis patients, IL-10 levels were increased prior to real acupuncture, placebo acupuncture or non-treatment. In the acupuncture group IL-10 was reduced, whereas IL-2

was hardly affected and IL-6 remained unchanged after therapy. In rheumatoid arthritis, IL-2 levels were lower than in the healthy controls<sup>36,37</sup>. After acupuncture, this reduced IL-2 production was elevated. In a rat model for ulcerative colitis,<sup>83</sup> acupuncture and moxibustion inhibited the expression of pro-inflammatory cytokines IL-1 $\beta$  and IL-6.

In conclusion, the (im)balance between T helper 1 cell-derived and T helper 2 cell-derived pro-inflammatory and anti-inflammatory cytokines was reset by acupuncture.

### Nitric oxide

As some observations highlight the stimulating effects of acupuncture to muscle afferents and blood flow through autonomic reflexes, the attributive effect of nitric oxide (NO) through local release and/or induction after electrostimulation should also be considered<sup>84</sup>. Significant and persistent increases in the arteriolar diameter were observed after electroacupuncture. This effect was abolished in the presence of nitro-L-arginine methyl ester (L-NAME), indirectly indicating that NO plays a key role in the primary mechanisms that are involved in microcirculation. From rat studies, it has been shown that NO levels were increased in rat striatum after cerebral artery occlusion, ischaemia and reperfusion. Electroacupuncture antagonised the ischaemia-elicited release of NO<sup>85</sup>. The anticonvulsant effect of electroacupuncture might be related to the decrease of the nitric oxide synthases neuronal nitric oxide synthase and inducible nitric oxide synthase<sup>86</sup>. From these preliminary results it is not clear whether central effects evoked by electro-acupuncture are more pronounced than those observed in the circulatory system, especially when inflammation occurs and the endothelial-derived nitric oxide synthase produces sustained amounts of NO<sup>87</sup>. Furthermore, a disturbed microcirculation through shunting of arterioles is also evoked by serotonin, another reasonable explanation why acupuncture could be (only) effective for the short-term treatment of migraine.

## DISCUSSION

### Pitfalls in methodology of measuring the use of acupuncture

In general, acupuncture trials include a limited number of patients. These trials are heterogeneous regarding patients, interventions and outcome measures and (therefore) present contradictory results. Most obvious is the need for well-designed and larger clinical trials<sup>88</sup>. Research in the area of complementary medicine such as acupuncture should be performed and evaluated at the same high-quality standards as research in the use of conventional therapies. In some studies, acupuncture points that were used in the placebo groups could be effective according to traditional Chinese medicine. Therefore, with regard to the standardised choice of acupuncture points in the set-up of repeatedly applied acupuncture in placebo acupuncture controlled clinical trials, the main problem to be solved is to determine the originally individualised treatment strategy that includes this approach.

A matter of debate is the set-up of randomised trials comparing placebo, placebo or non-treatment. A placebo needle has been designed, with which it could be possible to stimulate an acupuncture procedure without penetrating the skin<sup>89</sup>. In this set-up, placebo-treated patients experienced less 'de-Qi' pain sensation, also expressed by a diminished visual analogue scale pain. Another acceptable approach could be the inclusion of placebo laser acupuncture<sup>90</sup>, but it is preferred that placebo acupuncture is used, when not actively involved meridians are needled or superficial pricking is applied. Based on functional magnetic resonance imaging of the whole brain, it has however been demonstrated that superficial pricking revealed more signal intensity than minimal applied acupuncture<sup>91</sup>. From a pharmacotherapeutical point of view (kinetics, dynamics and dose finding), it is difficult to make comparisons between different acupuncture techniques that are used in not well-described studies. First, from traditional Chinese medicine, acupuncture should be considered and applied as an individually based therapy. Many factors and variables will influence the outcome of the therapy, such as: which of the acupoints and how many acupoints are chosen per treatment session? what is the reproducibility of the matrix of chosen acupoints? what is the type, depth, direction and manipulation of the inserted needle? what is the needle retention time and the length of the session? what is the frequency and total number of treatments? what is the follow-up? and what are the maintenance treatments?<sup>92</sup> (Table

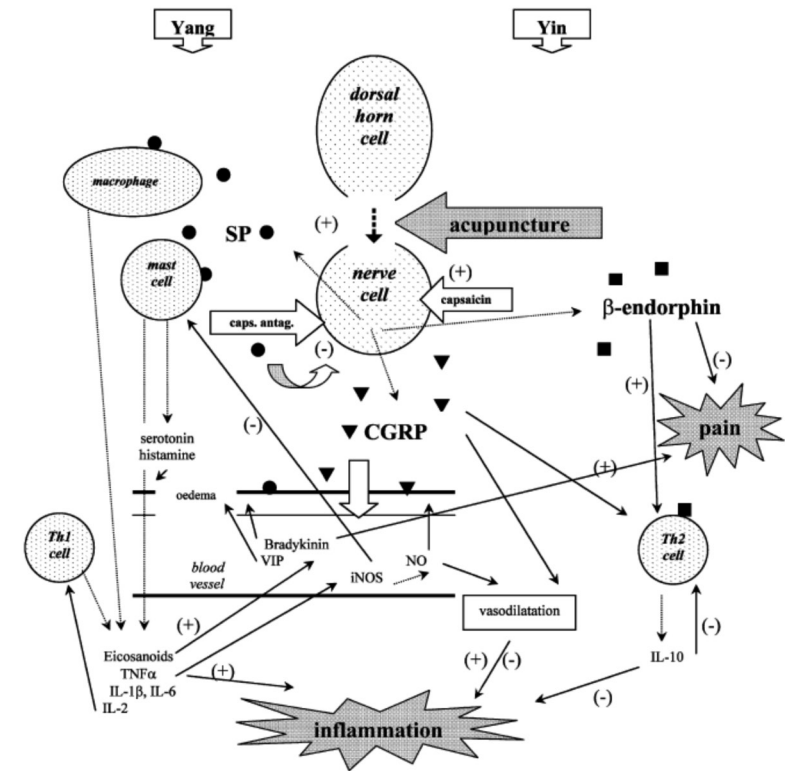


**Figure 1.** A number of studies describing the application of acupuncture in inflammatory disease have been published. Conclusions are difficult to be made, due to different acupuncture techniques used and insufficiently described methodology. (Drawing by Theodoor van Baars.)

3) Furthermore, for Western scientists, the main part of the literature describing Chinese and Japanese trials performed on acupuncture is only available as translated abstracts. Not only is there a marked difference between Chinese and Japanese acupuncture, but Western educated and qualified acupuncturists apply acupuncture differently in comparison with ancient acupuncturists. In some studies performed in Western countries, Chinese guest scientists collaborated in these studies, and they were the ones who performed the acupuncture treatments during their stay. As a consequence, some specific methodological information is missing, which makes it virtually impossible to continue or repeat treatment schedules for specific purposes (Fig. 1). Recently, standards for reporting the outcome of controlled acupuncture trials have been published<sup>93-96</sup>. Because the intensity and frequency of acupuncture as a complementary therapy will be individually chosen, one should also consider the subtype of the disease. In asthma, for instance, some aspects such as allergic, acute, chronic, exercise or cold-induced asthma should be considered, which will certainly affect the outcome of the acupuncture therapy. In most studies, subjective parameters (e.g. visual analogue scale pain, life questionnaires) are used. In open and single-blinded trials, the results clearly depend on the sample size and the number of repeated measurements. Objective parameters (e.g. forced expiratory volume in one second (FEV<sub>1</sub>), oedema or secreted volume and surface temperature) better reflect the attributive effect of acupuncture in the recovery from inflammatory diseases, but do not distinguish between primary and secondary events. Therefore, documented research on underlying mechanisms indicating the specific release or inhibitory action on the formation of inflammatory mediators such as substance P, CGRP,  $\beta$ -endorphin and cytokines would undoubtedly indicate whether acupuncture is advisable as a complementary therapy and confirm preliminary results.

### Mechanism of action of acupuncture: a concept

The underlying mechanism of acupuncture could be that, after antidromic stimulation of the nociceptor, CGRP, substance P and  $\beta$ -endorphin are all released. Initially, substance P will activate mast cells and in a later phase also macrophages to secrete inflammatory mediators. As a consequence, the mast cell will not only secrete serotonin and histamine, but also cytokines such as TNF- $\alpha$ . In turn, TNF- $\alpha$  could prime sensory nerve endings<sup>97</sup>. The activation of mast cells and mast cell-mediated inflammation is regulated by NO<sup>98</sup>. Macrophages will produce a number of cytokines and eicosanoids. In the blood vessel, CGRP will directly or indirectly affect vasodilation and extravasation via the stimulation of NO<sup>99,100</sup>. VIP and bradykinin. Delayed dilatation to bradykinin is cyclooxygenase-2 dependent<sup>101</sup>, whereas prostaglandin E<sub>2</sub> potentiates bradykinin and induces pain. Substance P regulates the vasodilator activity of CGRP through the action of proteases from mast cells<sup>14</sup>. In calcitonin/alpha calcitonin gene-related peptide knockout mice, nociceptive hypersensitivity was reduced<sup>102</sup>. Furthermore, it has been shown that both CGRP and VIP counteract nicotine-induced sweating<sup>103</sup>. The suppressing or potentiating effects of substance P and CGRP on metacholine-mediated cholinergic sweating, however, were dose dependent<sup>104,105</sup>. The ability of sweating to regulate skin temperature is well known and is more pronounced in men than in women. In women with chronic pelvic pain, intravenous infusion with CGRP resulted in a significant increase of skin temperature and complaints in comparison with healthy volunteers, whereas VIP did not provoke pain nor affect temperature<sup>106</sup>, suggesting the existence of a neurovascular disorder. There has been some evidence that hot flashes observed in menopausal women are due to up-regulation of CGRP receptors following ovarian hormone deficiency<sup>107</sup>. In ovari-ectomised rats, the greatest vasodilation and skin temperature increase was observed after CGRP, with less effect of VIP and the smallest effect seen after substance P<sup>108</sup>. In men who showed hot flashes after castration due to prostate carcinoma, plasma CGRP levels were elevated<sup>109</sup>. These results suggest that the vasodilative and skin temperature increasing effect of CGRP could be due to a diminished amount of (female) sex steroids. This could explain the higher incidence of migraine in woman<sup>110</sup> and menstrual-related migraine<sup>55,111</sup>, and the prevalence of some diseases in women, such as CRPS I<sup>47,48</sup> and carpal tunnel syndrome<sup>112</sup>. In addition, studies on gender differences in pressure pain threshold in healthy humans showed a significant decrease in females in comparison with males<sup>113</sup>.



**Figure 2.** Schematic overview of proposed interplay between nerve cells and inflammatory cells, and site of action of acupuncture and capsaicin or antagonists: role of neuropeptides, cytokines, nitric oxide and eicosanoids. NOS, Nitric oxide synthase; SP, substance P; Th, T helper.

In general, the acute, short-term and long-term effects of acupuncture are comparable with actions observed by the use of capsaicin. Capsaicin is the bioactive component of chili pepper. Application of capsaicin to the skin<sup>114-116</sup> or mucous membranes<sup>117</sup> initially results in irritation and hyperaesthesia. This momentary effect is attributed to the release of substance P from peripheral sensory C fibres. Repeated application of capsaicin would result in a depleted secretion of substance P from neurons. During inflammation these effects are more pronounced<sup>118</sup>. It is conceivable that the simultaneous release of CGRP will follow the same cascade of secretion. The antinociceptive effects of a capsaicin analogue, civamide, when given orally to rats, have been described<sup>119</sup>. Besides the receptor related effects of this vanilloid receptor agonist and neuronal calcium channel blocker, proposed actions

could also include inhibition of the neuronal release of CGRP and substance P<sup>120</sup>. That could explain the acute<sup>120</sup> and prophylactic properties<sup>121</sup> of this substance in the treatment of cluster headaches. In concordance with these findings, therapeutic (needle) acupuncture induces peripheral events that might improve tissue function and induce local pain relief, based on mechanisms that include axon reflexes, release of neuropeptides such as CGRP, anti-inflammatory actions of neuropeptides like substance P, and local release of  $\beta$ -endorphin. Furthermore, sympathetic inhibition could occur and levels of stress hormones and sex steroids could be reduced. Intense and frequently applied acupuncture gives rise to more pain, which could be due to high amounts of secreted CGRP (comparable with initial effects of capsaicin) when the inflammatory effect is predominant. Pain relief sometimes is observed after some days of treatment, possibly due to the delayed release of  $\beta$ -endorphins and the accumulated dose needed to be effective<sup>2</sup> through IL-10 formation<sup>79,122-124</sup>. IL-10 formation is limited, as has been shown in IL-10-dependent T-cell populations<sup>80</sup>.

As already stated in the Introduction, high levels of CGRP have been shown to be pro-inflammatory but, on the contrary, CGRP in low concentrations exerts potent anti-inflammatory actions<sup>12</sup>. The main attributive effect of substance P could be the feedback regulation of CGRP release from nerve endings<sup>13,14</sup>. The effects of neuropeptides may vary from one organ or tissue to another. The presence and time-dependent contribution of mast cells, macrophages and other inflammatory cells to produce mediators that activate or counteract the inflammatory process may be of crucial importance<sup>125</sup> (Fig. 2). Therefore, a well-performed and frequently applied 'low-dose' treatment of acupuncture could provoke a sustained release of CGRP with anti-inflammatory activity, without stimulation of pro-inflammatory cells. That could be the explanation why acupuncture only seems to be beneficial in the treatment of some inflammatory conditions.

## CONCLUSIONS

A number of observations on the anti-inflammatory actions of acupuncture have been published, representing open studies and randomised trials. Both short-term and long-term treatment schedules were performed, with varying number of acupuncture points, acupuncture frequency and additional application of electro-stimulation. The value of complementary acupuncture in the treatment of inflammatory diseases is still questioned. In asthma, the highest effective rate observed was obtained after a high number of frequently applied acupuncture sessions were performed, then reduced, and then performed at least 10 times per year to prevent relapse<sup>15</sup>. In rhinitis, results that were mainly obtained from open trials suggest a complementary effect of acupuncture after allergen provocation. In inflammatory bowel disease and rheumatoid arthritis, the usefulness of acupuncture still has to be demonstrated in large randomised trials. In epicondylitis and CRPS I, the attributive immunosuppressive effect of acupuncture has not yet been properly investigated, although a reduction of pain has been observed. From preliminary results it is conceivable to hypothesise that CGRP has a prominent role in the acupuncture-affected regulation of acute, sub-acute and chronic inflammation, regarding the vasodilative properties of this neuropeptide. Substance P should be considered to counteract the release of CGRP from nerve endings, whereas the balance of the mast cell derived pro-inflammatory TNF- $\alpha$  and the T-cell derived anti-inflammatory IL-10 could contribute to the development of the chronic stage of the inflammation. In this respect, acupuncture as a maintenance treatment could be beneficial to reduce inflammation. Evidence from large randomised trials, including follow-up measurements of mediators of inflammation, both at the site of inflammation and in the periphery, should be obtained to prove the immunologic effects of acupuncture.

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Chapter **4**

**Complex regional pain syndrome  
type I may be associated with  
menstrual cycle disorders:  
a case-control study**

Ineke van den Berg  
Ylian S. Liem  
Feikje Wesseldijk  
Freek J. Zijlstra  
M.G. Myriam Hunink

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## SUMMARY

**Background** Complex regional pain syndrome type I (CRPS I) can develop after severe trauma or surgery in the limbs, and presents with chronic, changes in temperature, edema and dysfunction. Seventy-five percent of CRPS I patients are female. While neurological and inflammatory components have been proposed, the etiology remains unclear. No consensus on optimal management of CRPS I exists.

In traditional Chinese medicine, menstrual disorders are related to the state of women's constitution and therefore identify their pain patterns. A classification by constitution might improve the pain management in CRPS I patients. It is unknown whether associations exist between menstrual-cycle-conditions and CRPS I.

**Aim** To investigate whether a specified menstrual condition is associated with the risk of developing CRPS I.

**Methods** A population-based case-control study of CRPS I was conducted among Dutch women aged 18-82; i.e. 34 women with CRPS I and 147 controls. A standard questionnaire consisting of 59 menstrual-cycle-symptom-based questions was administered. From this questionnaire, 15 CRPS I-related questions (DRQ 15) were analyzed. We used multivariate logistic regression to obtain odds ratios and 95% confidence intervals (CI) for specified menstrual disorders adjusting for age, oral contraceptives, hysterectomy and age at menarche  $\leq 12$  and  $\geq 17$  years.

**Results** On the basis of the DRQ 15, women with CRPS I were 5.3 (95%CI 2.1, 12.9) times more likely to have menstrual disorders than comparable controls.

**Conclusion** Our results suggest that selected menstrual conditions are associated with the risk of developing CRPS I.

## INTRODUCTION

Complex regional pain syndrome type I (CRPS I, also known as reflex sympathetic dystrophy, Sudeck's dystrophy or posttraumatic dystrophy) is an extremely painful disorder of the soft tissues, which develops as a disproportionate consequence of traumas and is most common in the limbs<sup>1-3</sup>. It is marked by various autonomic and vasomotor disturbances such as diffuse pain, spreading edema, changes in temperature disturbances and impaired active range of motion<sup>4-7</sup>. CRPS I is diagnosed by the Bruehl criteria (Table 1) after exclusion of other reasons for the pain or dysfunction<sup>8</sup>. Established by consensus between clinicians and basic scientists, these criteria are practice-based rather than mechanism-based, which might be a reason for possible late recognition and treatment of CRPS I.

The number of persons suffering from chronic CRPS I in the Netherlands is estimated at 20,000; and effective treatment is not available<sup>9</sup>. Various theories concerning the patho-physiological mechanism of CRPS I have been proposed. A change in sympathetic activity<sup>10</sup>, inactivity<sup>11</sup>, neurogenic inflammation<sup>12</sup> and an inflammatory response<sup>13</sup> have all been suggested as possible originate mechanisms for CRPS I. Worldwide there seems to be a gender disposition to the effect that 75% of patients are women, with a median age of onset of 46 years. Menstrual cycle-related problems in the year before CRPS I developed are described<sup>14</sup>. An association between the development of CRPS I and cumulative endogenous estrogen exposure is not found<sup>15</sup>.

Nevertheless, as early as 1966, Von Zedlitz described the positive effects of sex hormones in the treatment of CRPS I<sup>16,17</sup>. In contrast to Von Zedlitz, Janson et al. described that postmenopausal women (age > 50) who received hormone replacement therapy reported more muscular pain than those without this therapy<sup>18,19</sup>. Furthermore, changes in estrogen are correlated with a variety of effects in the central nervous system (CNS), such as changes in pain transmission, headache, dizziness, nausea, temperature regulation, and mood. The fluctuating estrogen levels during ovarian cycles and over the lifespan therefore cause predictable changes in serotonin systems in women<sup>20,21</sup>.

To our knowledge, no study has been conducted on a possible association between CRPS I and specified menstrual disorders. We assumed there might be such an association from the point of view of traditional Chinese medicine (TCM) in which menstrual disorders can identify pain patterns. TCM takes a holistic approach to the management of chronic disease in relation to the patient's underlying condition and vital body energy (Chi)<sup>22,23</sup>. Thus, the chronic complaints in CRPS I may be linked to characteristics of other organ systems as predictors of clinical success; pattern recognition on the basis of diagnosis and therapy. This implies a shift of focus away from the disease process in a particular organ to the process in the whole organism or 'system'.

We report a pilot study aimed at investigating whether women's risk of developing CRPS I, as assessed by a specified TCM condition as proxy, is predicted through a validated TCM-questionnaire of the menstrual cycle and therefore is associated with described anomalies of the menstrual cycle in pre-menopausal women. If so, this questionnaire might provide an additional tool for the early diagnosis of CRPS I.

## METHODS

### Study population

In this population-based case-control study we included 34 women with CRPS I (mean age 48.8, range 19-68) and 147 women without CRPS I (mean age 44.5, range 18-82). The women in the case group had been referred to the pain clinic of Erasmus MC, the Erasmus University Medical Center, Rotterdam, the Netherlands after initial diagnosis by their GP. The diagnosis was confirmed by an anesthesiologist specialized in chronic pain management, who applied the Bruehl criteria (Table 1)<sup>1</sup>. These patients participated in several studies performed between 2001 and 2004 either to investigate the pathophysiology of CRPS I or the effects of specific treatments for it<sup>12,24</sup>. Exclusion criteria were a major trauma or systemic disease and CRPS I type 2 with causal nerve lesion. The control group was a convenience sample of women traveling on the same day on the Rotterdam subway, and who agreed to be interviewed when passing the gate of the subway station nearest to Erasmus MC. They had been matched for

the age distribution expected for women with CRPS I. In addition they had been matched for the past or present use of oral contraceptives, for the following reason. CRPS I typically develops after minor traumas such as bone fracture and sprains<sup>3</sup>. Oral contraceptive users appear to reach the menopause with a bone density 2-3% higher than that of non-users, and would therefore seem to be at lower risk<sup>25,26</sup>.

### Questionnaire and data collection

This study is part of a larger study about the effects of acupuncture on pain and skin temperature in patients with CRPS I. The Erasmus MC medical ethical review board approved the study, and all patients signed a written informed consent form.

The questionnaire was a forward/backward translation into the Dutch language of the German version of the TCM Questionnaire. It contained 59 items concerning six aspects of the menstrual cycle in a woman's fertile age<sup>27</sup>. The six aspects described (1) the menstrual cycle (8 symptom questions (sq)), (2) pre-menstrual syndrome (9 sq), (3) amount of blood loss (13 sq), (4) menstrual pain (9 sq), (5) color of the lips of the mouth (6 sq), and (6) other complaints (14 sq). Other complaints were questions about headache, flushes, palpitations, perspiration, cold hand and feet, urinating problems, loneliness, and hyperventilation. Eighteen additional questions addressed profession, general medical history, specific medical history of

**Table 1.** Criteria of Bruehl: Diagnostic criteria for Complex Regional Pain Syndrome type I

<b>Continuing pain</b> which is disproportionate to any inciting event <b>and</b>	<b>Exclusion</b> of other reasons for pain or dysfunction <b>and</b>	Patient reports presence of at least one <b>symptom</b> in each category <b>and</b>	Doctor reports at least one <b>sign</b> of two or more categories
Vasomotor: Temperature asymmetry and / or skin colour asymmetry			
Sensory: Hyperalgesia or allodynia			
Sudomotor / oedema: Oedema and / or sweating changes and / or sweating asymmetry			
Motor / trophic: Impairment of motor function, including weakness, tremor, and dystonia. Atrophy of the hair, nails, and other soft tissues. Alterations in hair growth. Loss of joint mobility and range of motion.			
4 Categories			

**Table 2:** Set 15 selected menstrual cycle symptoms questions, related to POS syndrome, and therefore CRPSI related.

Question	Yes CRPSI patients n=32, (%)	Yes Controls n = 147, (%)	p-value
<u>PMS:</u>			
<b>Do you suffer from headaches before menstruation?</b>	<b>19 (59.4)</b>	<b>50 (12.9)</b>	<b>0.008</b>
Are you tense, emotional or depressed before your menstruation?	12 (37.5)	37 (8.2)	0.156
<b>Do you have problems with constipation before your menstruation?</b>	<b>9 (28.1)</b>	<b>8 (6.1)</b>	<b>&lt;0.001</b>
<u>Menstrual Cycle:</u>			
Do your menstrual periods always start later (1-7 days) than the expected 28 days?	3 (9.4)	6 (2.0)	0.214
Do you have an extra craving for sweet food?	9 (28.1)	42 (6.1)	0.959
<u>Menstrual Pain:</u>			
<b>Do you have pain just before the menstruation?</b>	<b>22 (68.8)</b>	<b>46 (15)</b>	<b>&lt;0.001</b>
<b>Do you have pain during the menstruation?</b>	<b>21 (65.6)</b>	<b>68 (14.3)</b>	<b>0.030</b>
Do you have strong stinging pain during your menstruation?	11 (31.4)	34 (7.5)	0.099
<u>Amount of blood loss:</u>			
<b>Do you have heavy or prolonged bleeding?</b>	<b>19 (59.4)</b>	<b>49 (12.9)</b>	<b>0.004</b>
<u>Other menstrual complaints:</u>			
<b>Do you have headaches during menstruation?</b>	<b>20 (62.5)</b>	<b>39 (13.6)</b>	<b>&lt;0.001</b>
Do you suffer from insomnia during the menstruation?	7 (21.9)	18 (4.8)	0.112
<u>Other complaints:</u>			
Do you feel lonely?	4(13)	19 (2.7)	0.997
<b>Do you perspire / glow with heat at night?</b>	<b>16 (50)</b>	<b>42 (10.9)</b>	<b>0.019</b>
Do you suffer from heart palpitations?	9 (28.1)	28 (6.1)	0.179
<b>Do you suffer from cold hands or feet?</b>	<b>16 (50)</b>	<b>42 (10.9)</b>	<b>0.013</b>

CRPSI, oral contraceptive use, age at menarche, age at menopause, and hysterectomy.

IB and FJPMH administered the questionnaire about the menstrual cycle. The women in the case group received the questionnaire from the doctor and completed it at home, after their visit to the hospital. In an accompanying letter, the women were asked to recall their menstrual cycle before the use of oral contraceptives or before hysterectomy or other interventions, and before the last years of menopause. It is well known that bleeding pattern changes considerably over the last years before menopause. Controls completed the questionnaire on the spot.

### Outcome measure

On the basis of the literature, we assumed that the pattern most related to CRPSI would be painful obstructive syndrome (POS)<sup>23,28-30</sup>. In POS, only particular menstrual cycle related symptoms are to be taken into account. Prior to the analysis, a set of fifteen questions related to the POS syndrome (therefore CRPSI related) was selected from the full questionnaire (Table 2). Symptoms addressed in the questionnaire were noted as present or absent.

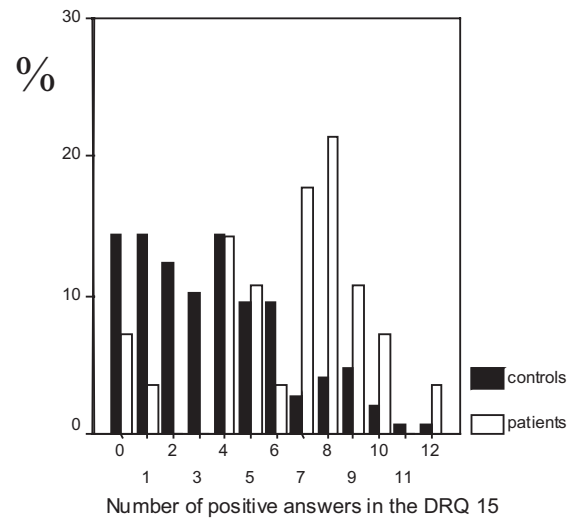
### Data analysis

The data were analyzed using SPSS 11.0 for Windows, SPSS Inc., Chicago, IL. Demographic characteristics of patients and controls were compared using the Mann-Whitney *U* test for age and the Chi-square test for oral contraceptive use.

We tested the hypothesis that women in the case group would have more symptoms than the control group. To dichotomize the measure of exposure, a cut-off point was determined from the distributions of numbers of positive answers of patients and controls in a histogram (Fig. 1). Because the distributions partly overlapped, the cut-off point was determined as the intersection of the distributions. After viewing the data, we defined a POS related menstrual syndrome if more than six questions of the set were answered positively. Mean number of positively scored menstrual symptoms was calculated for both groups.

Proportions of women with the menstrual syndrome were compared using odds ratios (ORs) and confidence intervals (CIs) as measures of association.





**Figure 1** Histogram of the total number of positive answers (in percentage) for the set of 15 symptoms.

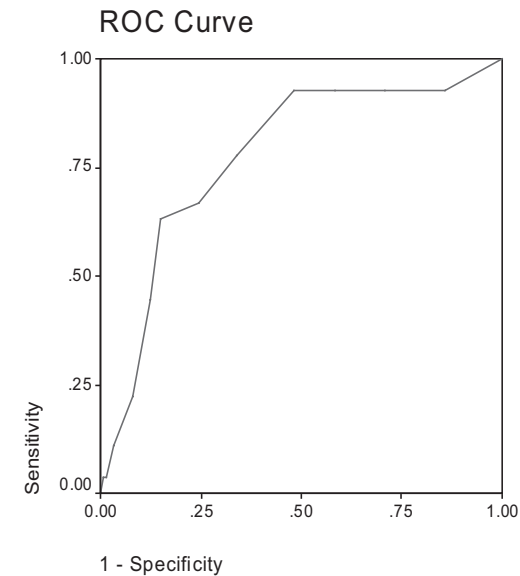
able) was adjusted for age, age at menarche ( $\leq 12$  and  $\geq 17$  years), current or past oral contraceptive use, and a history of hysterectomy. A  $p$ -value (two sided)  $\leq 0.05$  was considered to be statistically significant. Subgroup analyses were performed for the factors age  $\leq 50$  and age  $> 50$ , due to the age reference range expected for women with CRPSI<sup>9</sup>.

**Table 3.** Factors associated with diagnosis of confirmed CRPSI among questioned patients and controls.

	Cases	Controls	OR (95%CI)	P
>6 positive answers	18/34 (53%)	22/147 (15%)	6.4 (2.2–14.4)	< 0.001
Multivariate regression: age, age at menarche ( $\leq 12$ and $\geq 17$ years) current or past oral contraceptive use, and a history of hysterectomy			5.2 (2.1–12.9)	<0.001
Multivariate regression: 20 patients with age $\geq 50$ years			15.5 (4.4, 53.9)	< 0.001
Multivariate regression: 14 patients with age $\leq 50$ years			2.6 (0.8, 8.8)	0.06

Chi-square tests were performed to assess the relationship between the presence of the menstrual syndrome and the factors age  $\leq 50$ , hysterectomy, oral contraceptives and age at menarche  $\leq 12$ , and  $\geq 17$  years.

In multivariate logistic regression analyses, the relation between the presence of the menstrual syndrome (as dependent variable) and the presence of CRPSI (as independent variable)



**Figure 2** ROC curve for the set of 15 questions related to CRPSI, resulting in an area under the curve of 0.77. With a fixed cut-off value ( $>6$  positive answers), the sensitivity is 64% and the specificity is 85%.

We constructed a ROC curve with the number of positive answers as test variable and the Bruehl criteria as reference standard (Table 1). Sensitivity and specificity of the selected set of questions were calculated for scores higher than the cut-off value of six positive answers. Subsequently we calculated the area under the curve to compare the discriminative ability of the set of questions with the reference standard.

## RESULTS

The case group and the control group did not significantly differ with regard to age ( $p = 0.17$ ) and oral contraceptive use ( $p = 0.86$ ).

The mean number of positively scored menstrual symptoms in the patient group was significantly higher than that in the control group: 6.4 (se 0.56) versus 3.6 (se 0.24) ( $p < 0.001$ ) (Fig. 1). Eighteen of the 34 women in the patient group (53%) gave more than six positive answers; versus 22 of the 147 in the control group (15%). The odds ratio of having more than six positively scored menstrual symptoms for patients compared to controls was 6.4 (95%CI 2.2–14.4,  $p < 0.001$ ). The univariate analyses revealed no significant relationship between the presence of the POS syndrome (more than six positive answers) and the factors: age  $\leq 50$  years, hysterectomy, use of oral contraceptives, and age at menarche  $\leq 12$  and  $\geq 17$  years. Multivariate logistic regression analysis revealed no significant effects for current

age, age at menarche ( $\leq 12$  and  $\geq 17$  years), current or past oral contraceptive use, or a history of hysterectomy. Adjusted for these covariates the OR was 5.2 (95%CI: 2.1-12.9,  $p < 0.001$ ).

Additional multivariate analysis with current age as an interaction term demonstrated that age was a significant effect modifier ( $p = 0.02$ ).

Analyses in the two subgroups according to age showed that the odds ratio was 15.5 (95%CI: 4.4, 53.9,  $p < 0.001$ ) in the group of patients ( $n = 20$ ) aged  $\geq 50$  years. The odds ratio for patients under the age of 50 years ( $n = 14$ ) was 2.6 (95%CI: 0.8, 8.8,  $p = 0.06$ ) (Table 3).

The ROC curve depicted in Fig. 2 shows an area under the curve of 0.77 in the selected set of questions, with a sensitivity of 64% and a specificity of 85% for the cut-off value of six positive answers.

## DISCUSSION

This pilot study is the first population-based case-control study in which the development of CRPSI was associated with anomalies of the menstrual cycle in pre-menopausal women. We investigated whether the risk of developing CRPSI is associated with 15 POS representing disorders of the menstrual cycle (DRQ 15). Overall, compared to controls, women with CRPSI were found to be significantly more likely to confirm more than six symptoms even after adjustment for age, age at menarche ( $\leq 12$ , and  $\geq 17$ ), oral contraceptives use and hysterectomy, with an adjusted odds ratio of 5.2. In addition, the ROC curves suggest that the DRQ 15 has a good discriminative power in women with CRPSI and can be used as additional tool for the early diagnosis and additional TCM treatment of CRPSI. Subgroup analyses showed that the association between CRPSI and the menstrual syndrome was stronger for women over 50 years of age.

Our findings suggest a close relationship between CRPSI and mood, physical and behavioral symptoms, of the sort described by Freeman and Bruehl as well as in Chinese medical textbooks<sup>31-33</sup>. Actual association between psychological and behavioral factors and CRPSI remain controversial because the lack of methodological high-quality studies. In the literature, the majority of studies showed no relation, although some studies have ob-

served psychological factors as anxiety, depression, somatisation and hypochondria in the maintenance of CRPSI<sup>34</sup>.

Disproportionate pain, related to menstruation has also been described in patients with mood and anxiety disorders, and women with fibromyalgia (FM)<sup>35-37</sup>. FM and CRPSI show similarities in age distribution, male-female ratio, pain characteristics and sensory signs and symptoms. In CRPSI, motor, autonomic and trophic changes are part of the criteria (Table 1), but only occasionally reported in FM<sup>38</sup>.

In the present study, 15% of women in the control group were classified as having menstrual disorders. Likewise, in a case control study by Freeman et al. 15% of controls had a highly positive score in the daily symptom report questionnaire on premenstrual symptoms<sup>31</sup>.

The difference in prevalence of chronic widespread pain between men and women cannot be explained by sex hormones alone<sup>21,35,39</sup>. For example, studies in rodents have shown differences in pain modulation systems of males and females<sup>40</sup>.

The Chinese medicine theory might provide another explanation for the adult female disposition in CRPSI. The penetrating vessel (Chong Mai), together with the directing vessel (Ren Mai) regulates the uterus and menstruation. The penetrating vessel controls all the blood connecting channels, and clarifies the connection between disharmony of blood in the uterus and the development of muscular pains. It also demystify why women are more prone to external invasions during menstruation: depletion blood in the penetrating vessel induces a vacuity of the blood connecting channels and therefore the space between the skin and muscles (Cou Li) becomes empty and assessable for invasion by external pathogenic factors caused by traumas<sup>41</sup>. Perhaps women who are familiar with excessive bleeding during their period, also experience more bleeding at injuries. When, e.g. the fractured limb is fixed in plaster, their ongoing bleeding causes internal pressure and maybe damage the soft tissues. Further examination of this theory is needed.

Several limitations of the study, which may have caused bias, need to be mentioned. First, the case-control design did not show the incidence of CRPSI to be estimated on the basis of our data. For the same reason, the OR may have been overestimated. Although the groups were comparable with respect to age and oral contraceptive use (Table 2), we adjusted for age, oral contraceptives, hysterectomy, and age at menarche. It may well

be that the effect observed was caused by other, unmeasured, differences between both groups. Third, the questionnaire used in this study has not yet been validated by Western criteria<sup>27</sup>. However, well trained traditional Chinese medicine practitioners use this questionnaire worldwide to identify the pattern of disharmony that prevails in patients with a particular pain condition<sup>42</sup>.

In order to keep information bias to a minimum, participants completed the whole questionnaire with the 59 symptoms rather than only the selected 15 disease-related symptom questions (DRQ 15). In addition, because participants were not aware of the study hypothesis, recall of exposure was probably not affected. In this pilot study we used a convenience sample for the controls, for several reasons. First, we wanted to find out if the menstrual cycle questionnaire, which may likely arouse shame, was a questionnaire that was fair and well to answer. Second, could we recruit volunteers of the target age for this survey? Further, it might be considered unwise to commit to an expensive full-fledged study if a postulated relationship is not first observed in a convenience sample. Nevertheless, the convenience sample data could weaken the results of our study.

Finally, not all women still had a menstrual cycle, or regulated their cycle was through the use of oral contraceptives. Our results may then have been influenced by recall bias.

The results of the subgroup analyses show a stronger association between CRPS I and the menstrual syndrome for of the over-50s. This result seems counterintuitive, since we would have expected older, post-menopausal women not to remember their menstrual cycle pattern as well as younger women did. We therefore expected to find a weaker association in the older age group. Chinese medicine theory might provide an explanation. The mean age of onset of CRPS I in women is 46 years<sup>19</sup>. At that time of their life, women are in their peri-menopausal period and have lost the positive healing effect of new blood production and powerful blood circulation related to menstruation. This, in combination with the natural energy-loss during lifetime, makes them more vulnerable to the development of CRPS I. However, regardless of the difference in OR between the older and younger women, the ORs were clinically relevant in both, although in the younger age group not statistically significant, possibly due to the low sample size of this group. Studies with larger samples are needed to confirm our findings for the different age groups. The finding of a clear association between more than six positive answers in

the DRQ 15 and the development of CRPS I should be interpreted cautiously, as the sample size was limited and therefore the CIs wide. Likewise, issues of replication and replicability deserve attention in further prospective studies considering CRPS I and additional menstrual variables.

For many years, attempts have been made to merge the Western and Chinese systems of medicine. However, for the merging process to have any clinical relevance, comparisons must be based on diagnostic and/or therapeutic similarities rather than on semantics. If practitioners proceed carefully, the two systems can enrich each other<sup>22</sup>. The diagnosis of CRPS I, which is still practice-based, could be further differentiated by using TCM diagnostic methods.

In conclusion, in this pilot study we successfully demonstrated that defined menstrual disorders are associated with the development of CRPS I. The results of our study suggest a menstrual-cycle-related imbalance in the constitution of women with CRPS I, notably those aged over 50. This may also explain the predisposition of menopausal women to CRPS I.

A validation study of the usefulness of the DRQ 15 is an essential next step. Selected menstrual disorders should be considered, and a menstrual cycle history should be included in the evaluation of chronic CRPS I patients. The traditional Chinese medicine questionnaire used in this study could contribute to the early recognition and diagnosis of female CRPS I patients.

## ACKNOWLEDGEMENTS

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Chapter **5**

**Natural History of  
Breech Presentation:**

**Prognostic Value of Ultrasound  
in the Generation R study**

Ineke van den Berg  
Lidia R. Arends  
Eric A. P. Steegers  
Vincent W.V. Jaddoe  
M.G. Myriam Hunink  
Johannes J. Duvekot

*Submitted for publication*



## ABSTRACT

**Objectives** To describe the natural history of singleton breech presentation in a cohort study and determine the value of ultrasound in predicting nonvertex delivery. Ultimately this could help define the optimal time window during which effective preventive version strategies can be performed to avoid nonvertex presentation at birth.

**Methods** The study was embedded in the Generation R Study, a prospective cohort study from early fetal life onward, of 7135 singleton pregnancies. Ultrasound at approximately 20 and 30 weeks of gestation was performed to establish the fetal position. Odds ratios and sensitivity and specificity of ultrasound in predicting nonvertex presentation at delivery were calculated.

**Results** Of 7135 pregnancies, 3315 (46.5%) were in a nonvertex position at 20 weeks decreasing to 1259 (17.6%) at 30 weeks and 307 (4.3%) at delivery. Fetal position at 20 weeks was not predictive of nonvertex presentation at birth (OR 1.1, 95% CI 0.89 to 1.41,  $p = 0.33$ ). Ultrasound-confirmed nonvertex position around 30 weeks was highly predictive of nonvertex presentation at delivery (OR 28.45, 95% CI 20.96 to 38.62,  $p < 0.0001$ ; sensitivity and specificity 83.0% and 85.3%), especially in nulliparous women (OR 53.97, 95% CI 36.1-80.8,  $p < 0.0001$ ) and preterm deliveries (OR 47.89, 95% CI 18.28 - 125.49,  $p < 0.0001$ ).

**Conclusion** Fetal ultrasound findings at 30 weeks were highly predictive, ultrasound at 20 weeks showed no value in predicting nonvertex presentation at delivery.

The presence of an ultrasound -confirmed breech position around 30 weeks could be used as an indication to monitor the fetal position and consider the use of version strategies, which can be performed safely and effectively.

**Keywords** nonvertex, breech, fetal presentation, ultrasound, prediction, sensitivity and specificity

## INTRODUCTION

Little is known about the natural behaviour of the fetus in utero, especially regarding the preferred fetal position. There are three main presentations of the fetus: cephalic (or vertex), nonvertex transverse and nonvertex breech. In pregnancies at term a nonvertex position is seen in about 3-4% of singleton fetuses, with a constant incidence over time<sup>1-4</sup>.

After it was demonstrated that planned cesarean section lowered neonatal mortality and morbidity compared with planned vaginal delivery for the term fetus in breech position<sup>5</sup>, cesarean section became more common practice for term breech delivery in many countries<sup>6</sup>. However, cesarean section is not without direct maternal risks<sup>7-8</sup>. Additionally, in subsequent pregnancies, there is an increased risk of adverse events like scar dehiscence or uterine rupture and abnormal placentation<sup>9-14</sup>.

Ultrasound examination during pregnancy is a useful diagnostic tool to identify fetal and placental anomalies, to follow fetal growth and to determine fetal and placental position and is considered safe in pregnancy<sup>15</sup>. Ultrasound is usually performed at different stages of gestation and provides different levels of detail at different stages. The fetal position is routinely determined from the first trimester onwards. An impressive cohort study, with inclusion data between 1987-1991, examined the natural history of fetal position throughout pregnancy using ultrasound and reported that a nonvertex fetus at 35 weeks had a 45% chance of spontaneous version by the time of delivery<sup>1</sup>.

During the course of pregnancy, the fetus turns more and more into vertex position. Prior to 32 weeks of gestation, spontaneous version of the fetus to vertex position occurs more frequently than after 32 weeks<sup>4, 16-17</sup>. Many possible physiologic mechanisms may lead to (persistent) breech position. At present, several interventions are in use to promote version of the fetus into nonvertex position in order to prevent nonvertex presentation at delivery. The major evidence-based approaches to correct nonvertex presentation before delivery are breech version acumoxa (BVA) performed between 33 and 36 weeks<sup>12</sup> and external cephalic version performed between 36 and 40 weeks of gestation<sup>18</sup>. Better understanding of the natural pathway of fetal position could give insight into the optimal timing of these interventions in case of nonvertex position.

We hypothesized that an additional ultrasound around 30 weeks gestational age predicts the probability of nonvertex presentation at delivery. This offers the opportunity to monitor the fetal position and guide the use of specific prenatal care that may correct nonvertex position, provided these can be performed safely and effectively.

The aim of our study was to describe the natural history of nonvertex presentation in a large cohort study and to determine the value of ultrasound performed at 20 and 30 weeks of gestation in predicting nonvertex delivery.

## METHODS

### Design and setting

The present study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life until young adulthood in a multi-ethnic urban population in Rotterdam, the Netherlands. The cohort comprises 9778 mothers and their children born between April 2002 and January 2006<sup>19-20</sup>. The study was approved by the Medical Ethics Committee of Erasmus University MC, Rotterdam. Written informed consent was obtained from all participants. Data on fetal ultrasound studies were collected prospectively. Gestational age was established based on the first ultrasound. Pregnant women were subsequently examined twice during pregnancy, in mid (18-24 weeks) and late (> 25 weeks) (mean 30 weeks, range 25 – 32 weeks) gestation. The individual time schemes depended on the specific gestational age at enrollment as described previously<sup>21</sup>. Eighty-eight per cent of ultrasound examinations were performed in a research setting at a regional health facility in Rotterdam; 12% in one of five hospitals in the vicinity under guidance of Generation R staff.

Although ECV was not protocolized in our cohort, subgroup analyses were performed to evaluate the number of women with a fetus at 36 weeks gestation followed in the Erasmus MC to whom the ECV was offered and performed, including the treatment effect.

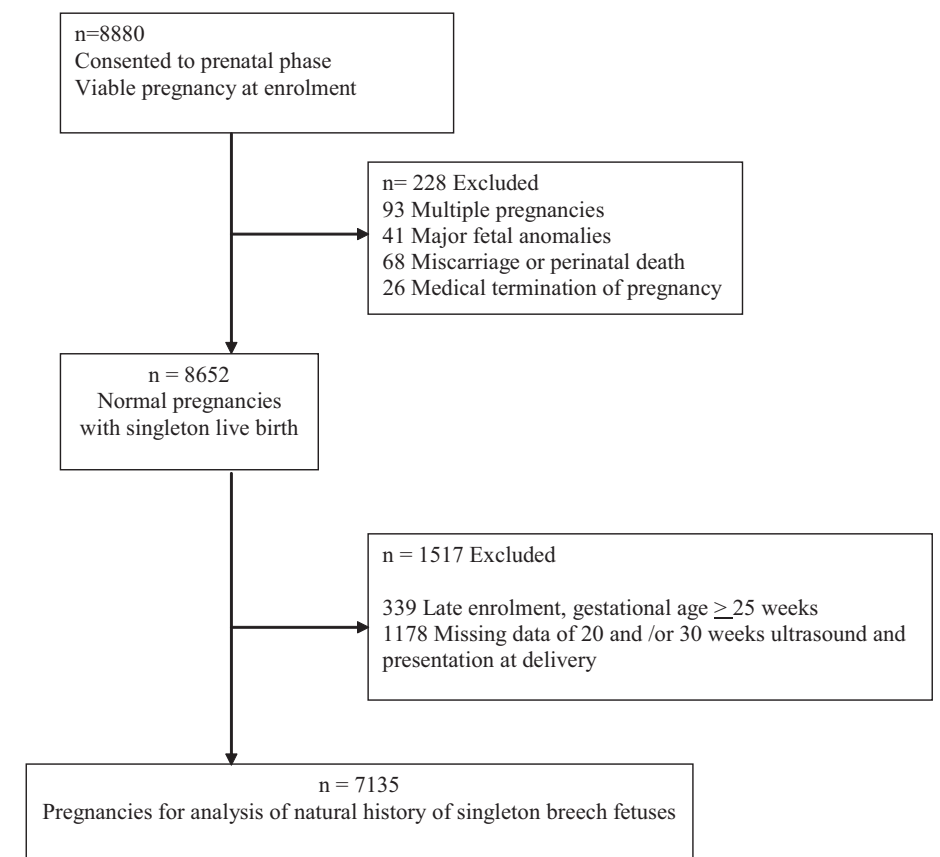
### Data collection

Of the 9,778 mothers participating in the Generation R Study, 91% (n=8,880) were enrolled during pregnancy<sup>15</sup>. Participants in the present

study were recruited from these 8,880 individuals (Figure 1). The inclusion criterion was a viable singleton pregnancy at enrolment. Exclusion criteria were the following: major fetal anomalies, gestational age  $\geq 25$  weeks at enrolment, missing data of the 20 and /or 30 weeks ultrasound, and missing data of fetal presentation at delivery. If more than two ultrasound examinations were performed we used findings from those carried out at the initially scheduled visits of 20 and 30 weeks of gestation.

Ultrasound examinations of the fetal position were performed using an Aloka® model SSD-1700 (Tokyo, Japan) or the ATL-Philips® Model HDI 5000 (Seattle, WA, USA).

**Figure 1.** Flow chart of inclusion of participants in the substudy of the Generation R longitudinal cohort.



The ultrasound examination of the fetal position was part of a more comprehensive exam in which fetal abnormalities were determined. In the Netherlands, in low risk pregnancies, only one ultrasound is offered around 20 weeks of gestation. All sonographers were experienced and underwent additional training according to the guidelines from the Fetal Medicine Foundation to achieve optimal reproducibility<sup>15, 20</sup>.

The presentation at birth was documented by the midwife or gynecologist who attended the delivery. For all participants it was known whether the pregnancy resulted in live birth, miscarriage, stillbirth, neonatal death or elective termination. Fetal position at delivery was known for 99.8% of these pregnancies. Breech and transverse presentation were combined as nonvertex presentation, since usually delivery will be performed by cesarean section<sup>22</sup>. In this study, deliveries were defined as preterm if they took place after the 30 weeks ultrasound and before 37 weeks of gestation.

### Statistical methods

The primary endpoint was nonvertex presentation at delivery. In predicting breech and transverse presentation at delivery the ultrasound findings at 20 weeks and 30 weeks were considered.

For type of presentation, we calculated odds ratios (ORs), and 95% confidence intervals (CIs), as well as p values. Statistical significance was set at a level of  $\alpha = 0.05$ . To determine the clinical performance of both ultrasounds, we used five statistical assessments: pretest probability, sensitivity, specificity, positive predictive value, and negative predictive value. Sensitivity was defined as the fraction of nonvertex presentations at delivery that was predicted correctly by the ultrasound examination, whereas specificity was defined as the fraction of cephalic presentations at delivery that was predicted correctly. Positive predictive value was defined as the probability of a non-vertex presentation at delivery conditional on a non-vertex position on ultrasound. Negative predictive value was defined as the probability of a vertex presentation at delivery conditional on a vertex position on ultrasound. Subgroup analysis was performed for nulliparous versus multiparous pregnancies, and for preterm versus term delivery. Statistical analysis was performed with SPSS version 17 for Windows (SPSS Inc, Chicago, IL, USA).

## RESULTS

Of the 7135 singleton pregnancies studied, 307 (4.3%) had a nonvertex presentation at delivery: 297 breech (4.2%) and 10 transverse (0.1%). Figure 2 shows the natural history in detail of the fetal presentation during pregnancy, i.e. position at 20 weeks, 30 weeks and the presentation at delivery overall. Of the 7135 pregnancies, 3315 (46.5%) were in a nonvertex position at 20 weeks decreasing to 1259 (17.6%) at 30 weeks and 307 (4.3%) at delivery.

**Table 1.** Performance values of ultrasound in predicting nonvertex position at delivery based on nonvertex presentation at 20 or 30 weeks of gestation (n= 7135)

	OR (95% CI)	Test probability (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
20 weeks of gestation	1.12 (0.89-1.40)	2.1	49	54	5	96
-Nullipara (n = 4015)	1.40 (1.07 -1.84)		52	57	5	96
-Multipara (n = 3072)	0.73 (0.47 - 1.13)		42	50	4	95
30 weeks of gestation	28.45 (20.96 - 38.62)	4.3	83	85	20	99
-Nullipara ^ (n=4015)	53.9 (36.07-80.76)		87	89	27	99
-Multipara ^ (n= 3072)	10.93 (6.70-17.82)		72	81	15	99
-Term delivery ≥36 weeks (n= 6982)	27.80 (20.10-38.45)		83	85	19	99
-Preterm deliv- ery <36 weeks (n=153)	60.00 (15.42-233.47)		84	90	60	98

OR: Odds Ratio

CI: Confidence interval

Test probability : the proportion of patients with the target disorder, out of all the patients with the symptoms(s), both those with and without the disorder:  $P(D+) = D+ / (D+ + D-)$  where D+ indicates the number of patients with target disorder, D- indicates the number of patients without target disorder, and P(D+) is the probability of the target disorder.

PPV: Positive Predictive Value.

NPV: Negative Predictive Value.

**Table 2.** Combinations of presentation during the natural pathway of the singleton pregnancies.

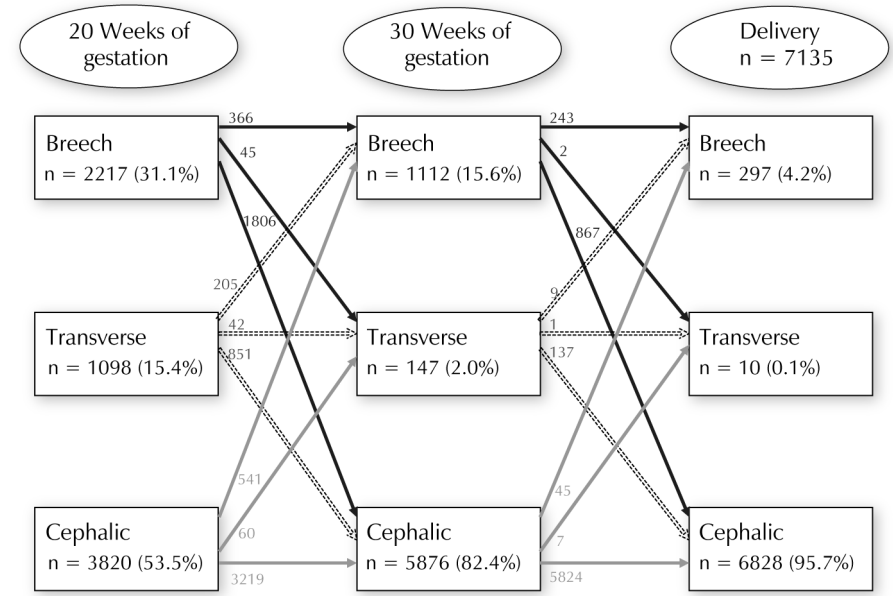
Presentation Fetus	All (100%) n = 7135		Nulliparae n = 4015*		Multiparae n = 3072*		Term delivery n = 6982 (97.9%)		Preterm delivery n = 153 (2.1%)	
	20 weeks	30 weeks	20 weeks	30 weeks	20 weeks	30 weeks	> = 36 weeks	< 36 weeks	> = 36 weeks	< 36 weeks
US	N	N	128 (1.8%)	101 (2.5%)	27 (0.9%)	117 (1.7%)	117 (1.7%)	11 (7.2%)	117 (1.7%)	11 (7.2%)
US	C	N	127 (1.8%)	94 (2.3%)	33 (1.1%)	120 (1.7%)	120 (1.7%)	7 (4.2%)	120 (1.7%)	7 (4.2%)
US	N	C	23 (0.3%)	15 (0.4%)	8 (0.3%)	23 (0.3%)	23 (0.3%)	0 (0%)	23 (0.3%)	0 (0%)
US	C	C	29 (0.4%)	14 (0.3%)	15 (0.5%)	26 (0.4%)	26 (0.4%)	3 (2.0%)	26 (0.4%)	3 (2.0%)
US	N	N	530 (7.4%)	211 (5.3%)	316 (10.3%)	526 (7.5%)	526 (7.5%)	4 (2.6%)	526 (7.5%)	4 (2.6%)
US	C	N	474 (6.6%)	209 (5.2%)	260 (8.5%)	466 (6.7%)	466 (6.7%)	8 (5.2%)	466 (6.7%)	8 (5.2%)
US	N	C	2634 (36.9%)	1432 (35.7%)	1179 (38.4%)	2578 (36.9%)	2578 (36.9%)	56 (36.6%)	2578 (36.9%)	56 (36.6%)
US	C	C	3190 (44.7%)	1939 (48.3%)	1234 (40.2%)	3126 (44.8%)	3126 (44.8%)	64 (41.8%)	3126 (44.8%)	64 (41.8%)
Total %			100%	100%	100%	100%	100%	100%	100%	100%

\*48 missings (0.7%) in parity  
 US = ultrasound  
 US 20= US around 20 weeks gestation  
 US 30= US around 30 weeks gestation  
 C=Cephalic presentation  
 N= Nonvertex, thus breech and transverse presentation

Table 1 shows the ultrasound performance measures of all women at 20 weeks and at 30 weeks of gestation in order to predict nonvertex presentation at birth. In the same table, the results of subgroup analyses are presented performed on the ultrasound performance measures at 20 and 30 weeks of gestation overall and in the subgroups of nulliparae and multiparae. Parity was known in 7087 (99.3%) of pregnancies. Of all cephalic presentations at delivery (n=6828), 5824 (85.3%) already had a cephalic position at 30 weeks of gestation (Table 2). Of all nonvertex presentations at delivery (n=307), 255 (83.1%) already had a nonvertex position at 30 weeks of gestation (Table 2).

There were differences between nulliparous (n=4015) and multiparous pregnancies (n=3072): 4.8% (n= 195) of the nulliparae vs. 2.0% (n= 60) of the multiparae had a nonvertex presentation both at 30 weeks of gestation and at delivery, whereas 0.7% (n= 29) vs. 0.8% (n=23) had a cephalic presentation at 30 weeks of gestation and delivered in nonvertex presentation. Of the nulliparae, 10.5% (n=420) had a nonvertex position at 30 weeks of gestation versus 18.8% (n=576) of the multiparae, and had turned to cephalic presentation before delivery.

**Figure 2.** The natural history in detail of the fetal presentation during pregnancy, i.e. position at 20 weeks, 30 weeks and the presentation at delivery overall.



Of all included pregnancies ( $n=7135$ ), 6982 (97.9%) delivered at term and 153 (2.1%) at  $< 36$  weeks of gestation. Table 1 also shows the ultrasound performance measures at 30 weeks of gestation for nonvertex presentation at delivery subdivided for preterm and term delivery, with the highest odds ratio for preterm delivery. (OR 60.00, 95%CI 15.42-233.47).

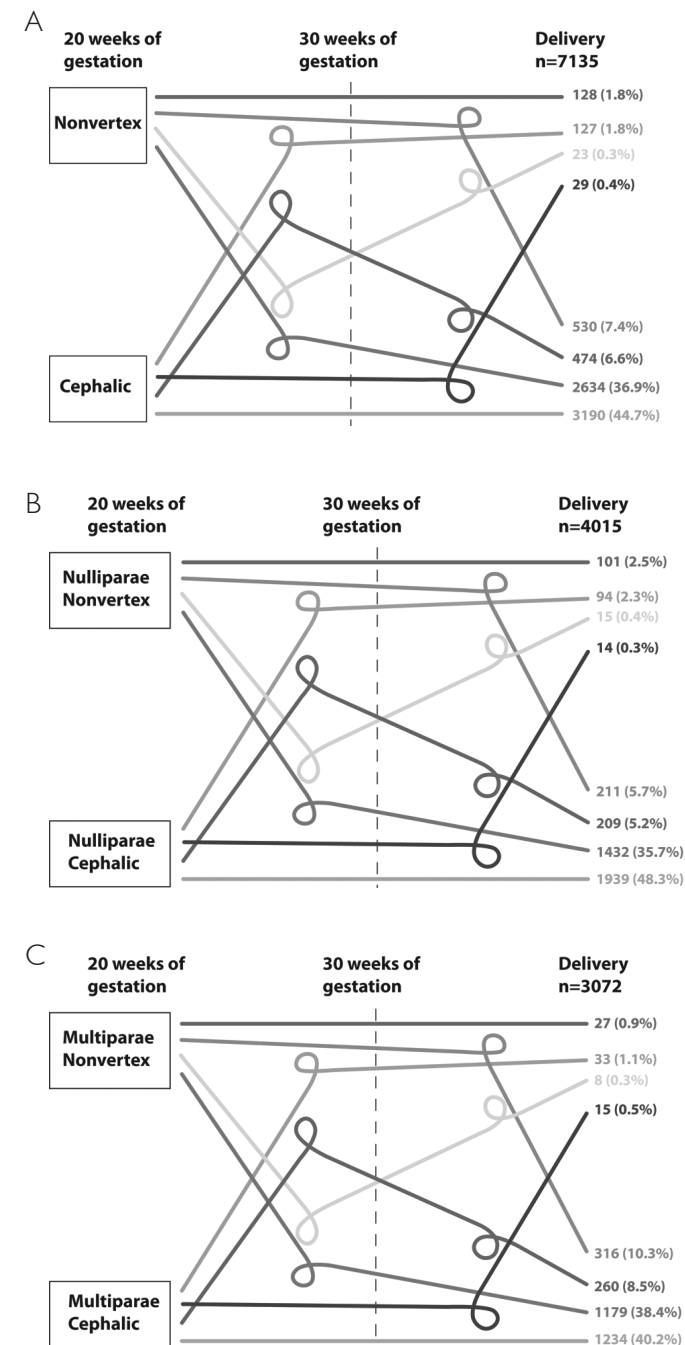
Using the ultrasound performance measures at 20 weeks of gestation compared with the ultrasound performance measures at 30 weeks of gestation, the percentage of missed nonvertex presentations (proportion false negatives, 1-sensitivity) was 51% versus 17% with a corresponding probability of a nonvertex presentation at delivery following a negative ultrasound of 4% versus 1%. The post-positive-test probability of nonvertex at delivery is 5% versus 20%. The p-values of all ultrasound performance measures at 30 weeks of gestation were highly significant, i.e. smaller than 0.0001 for all calculated odd ratios (Table 1), whereas the p-values of the measures at 20 weeks were not significant.

Subgroup analysis showed that, of the 1259 nonvertex fetuses at 30 weeks, 256 were observed in the Erasmus University Medical Center. Only 16 of these women were offered an ECV at 36 weeks of gestation, and one resulted in cephalic presentation at term.

In contrast with figure 2, figure 3a, b, c and table 2 presents individualized details on the various combinations of position during pregnancy, i.e. position at 20 weeks, 30 weeks and the presentation at delivery. During pregnancy, the fetal position of 3318 (46.5%) fetuses did not change, whereas 128 (1.8%) already had a nonvertex presentation at 20 and 30 weeks of gestation. The latter number is 41.7% of all neonates born in nonvertex presentation. However, of all nonvertex positioned fetuses at 20 weeks ( $n=3315$ ) only 3.9% was nonvertex at birth.

## DISCUSSION

This study evaluated the fetal position determined by ultrasound throughout pregnancy and the prevalence and the course of the nonvertex position in the Generation R study. We found that determination of the fetal position by ultrasound at 20 weeks of gestation does not predict fetal presentation at delivery. However, the examination at 30 weeks of gestation has substan-



**Figure 3** Individualized details on the various combinations of position during pregnancy, i.e. position at 20 weeks, 30 weeks and the presentation at delivery. a) all study participants. b) nulliparous women. c) multiparous women.

tial ability to predict nonvertex presentation at delivery, and may have an impact on prenatal decision making. We found clear statistically significant differences between nulliparae and multiparae with regard to the individual presentations during pregnancy.

Since a nonvertex position on the 30 weeks ultrasound is highly predictive of fetal presentation at delivery, it appears valuable as the initiating moment for interventions that elicit version of the nonvertex fetus and prevent nonvertex presentation at delivery, notably moxibustion, external cephalic version (ECV), hypnosis, or other complementary and additive therapies<sup>23</sup>. The most frequent physiological fetal movement during pregnancy is from nonvertex into vertex presentation<sup>24</sup>. Few studies have been performed to evaluate the value of ultrasound performed during pregnancy to predict nonvertex presentation at delivery<sup>1</sup>, and most studies were retrospective, and /or dated<sup>25-26</sup> or assessed after 28th<sup>27</sup> or 31st week of gestation<sup>28</sup>. It is suggested that spontaneous version is completed by the 37th week of pregnancy: no further spontaneous movement is likely to occur after this time because of the size of the fetus in relation to the size of the uterus<sup>25, 29-30</sup>. Others are of the opinion that spontaneous version of a nonvertex position at 35 weeks of gestation is still likely<sup>1</sup>.

One of the areas of research in the Generation R study is designed to identify early developmental problems in the child. Although the prevalence of nonvertex at delivery is low, pregnancies involving nonvertex presentations and nonvertex deliveries have a higher incidence of complications than pregnancies with vertex presentations<sup>6, 31</sup>. Some intrinsic factors that may be responsible for nonvertex presentation at delivery, such as placental, uterine or fetal anomalies<sup>32</sup>, can be identified with the additional ultrasound at 30 weeks<sup>1, 15</sup>. Decision criteria for implementing an extra ultrasound as a screening test for every pregnant woman at 30 weeks gestation, performed by experienced sonographers, should include test accuracy, cost of screening, and the prevalence and natural history of the disease. Test accuracy (sensitivity, negative predictive value, specificity, and positive predictive value) was demonstrated by our findings (Table 1 and 2).

Reducing nonvertex presentation in the population leads to fewer cesarean sections and fewer complications in both the mother and the newborn. Previously we modeled costs and benefits of moxibustion treatment in women with ultrasound-confirmed nonvertex presentation. It appeared that if 16% or more women offered Moxa complied, it was more effective

and less costly than expectant management of the nonvertex presentation<sup>33</sup>. Additionally, both the American College of Obstetricians and Gynecologists (ACOG) and the British Royal College of Obstetricians and Gynecologists (RCOG) recommend that all women with an expected uncomplicated nonvertex pregnancy at term should be offered ECV<sup>34-35</sup>. This procedure is successful in 50 to 60% of cases and is usually performed by a gynecologist as of 36 weeks gestation<sup>36-37</sup>. On the other hand, ECV may have serious complications, such as perinatal death and need for emergency cesarean delivery.<sup>30, 38-40</sup> Also, a spontaneous reversion rate of 3% has been reported. In addition, ECVs generate costs. Not all women will accept ECV treatment: reported rates of maternal refusal of ECV range from 18 to 76%<sup>41</sup>. Conversely, proportions of women potentially suitable for ECV who were not offered treatment range from 4 to 33%.<sup>42-43</sup> Interestingly, during the study period, ECV was not routinely in use in the Netherlands. Unfortunately, data on ECV were not uniformly recorded in this study and therefore, possible undertaken ECV's were not known for the whole population. Our subgroup analysis showed that during the study period, ECV was not offered as widely as advised and not really successful in a university teaching hospital. Therefore, we concluded that in our cohort ECV was only rarely offered and infrequently successful. Inclusion of the ECVs, however, might well have given greater weight to the argument made.

We have shown the highly predictive value of ultrasound findings at 30 weeks of gestation for predicting the presentation at delivery. Further investigation into the risk factors and potential mechanisms of nonvertex presentation is indicated. We recommend close monitoring of women with known or suspected risk factors for a persistent nonvertex presentation. Moreover, investigators should explore the possibilities of external cephalic version and acupuncture-type interventions in order to avoid a nonvertex presentation at term<sup>33</sup>.

Early recognition of atypical presentation could lead to a new strategy for preventive measures in mothers at high risk for nonvertex delivery, and possible extra care and follow up of the fetus. Especially in developing countries, where the number of children per mother is high and the public health system is more precarious, these relatively inexpensive and safe interventions could support maternal and child care.

Further research should focus on preventive strategies for known predictors for nonvertex presentation at delivery, so as to ensure a good start of



the newborn's life and good health for the mother. In this way, fetal and maternal morbidity and mortality could be reduced.

## CONCLUSION

In the Generation R study, the 20 weeks fetal ultrasound findings showed no predictive value for nonvertex presentation at delivery. The ultrasound at 30 weeks of gestation, however, was highly predictive of nonvertex presentation at delivery. The presence of an ultrasound-confirmed breech position of the fetus around 30 weeks of gestation could be used as an indication to monitor the fetal position and consider the use of version strategies provided these can be performed safely and effectively. Further research is needed to evaluate the effectiveness of these additional preventive therapies.

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Chapter **6**

**Effectiveness of acupuncture-type interventions versus expectant management to correct breech presentation: A systematic review**

Ineke van den Berg  
Johanna L. Bosch  
Ben Jacobs  
Irene Bouman  
Johannes J. Duvekot  
M.G. Myriam Hunink

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## SUMMARY

**Objective** A systematic review of studies assessing the effectiveness of acupuncture-type interventions (moxibustion, acupuncture, or electro-acupuncture) on acupuncture point BL 67 to correct breech presentation compared to expectant management, based on controlled trials.

**Data sources** Articles published from 1980 to May 2007 in databases of Medline, EMBASE, the Cochrane Central Register of Controlled Trials, AMED, NCCAM, Midirs and reference lists.

**Study selection** Studies included were original articles; randomised controlled trials (RCT) or controlled cohort studies; acupuncture-type intervention on BL 67 compared with expectant management; ultrasound confirmed breech presentation and position of the fetus after treatment confirmed with ultrasound, position at delivery, and/or the proportion of caesarean sections reported.

**Data extraction** Three reviewers independently extracted data. Disagreements were resolved by consensus.

**Data synthesis** Of 65 retrieved citations, six RCT's and three cohort studies fulfilled the inclusion criteria. Data were pooled using random-effects models. In the RCT's the pooled proportion of breech presentations was 34% (95% CI: 20-49%) following treatment versus 66% (95% CI: 55-77%) in the control group (OR 0.25 95% CI: 0.11-0.58). The pooled proportion in the cohort studies was 15% (95% CI: 1-28%) versus 36% (95% CI: 14-58%), (OR 0.29, 95% CI: 0.19-0.43). Including all studies the pooled proportion was 28% (95% CI: 16-40%) versus 56% (95% CI: 43-70%) (OR 0.27, 95% CI: 0.15-0.46).

**Conclusions** Our results suggest that acupuncture-type interventions on BL 67 are effective in correcting breech presentation compared to expectant management. Some studies were of inferior quality to others and further RCT's of improved quality are necessary to adequately answer the research question.

## INTRODUCTION

In pregnancies at term, 3-4% of singleton fetuses present by the breech<sup>1,2</sup>. Since the results of the Term Breech Trial in 2000 demonstrated a reduction in infant mortality and morbidity with planned caesarean sections compared with planned vaginal delivery in fetuses in breech presentation, caesarean sections have become common practice in many Western Countries for term breech deliveries<sup>3-9</sup>. An increase in caesarean sections for breech position, however, has distinct disadvantages including an increased risk of maternal urinary tract infection, haemorrhage, wound infection, and scar dehiscence or uterine rupture during subsequent labour and higher costs<sup>10</sup>. Another, non-invasive, method to correct breech presentation comes from traditional Chinese medicine (TCM), which involves the activation of acupuncture-point Zhiyin, Bladder 67 (BL 67)<sup>11-13</sup>; BL 67 is located beside the outer proximal corner of the toenail of the fifth toe (Fig. 1). In 1984, a controlled cohort trial of the Cooperative Research Group in China, reported that the proportion of cephalic presentations following treatment was 81% in the intervention group ( $n = 241$ ) versus 49% in the control group ( $n = 264$ )<sup>14</sup>. Since this Chinese study, various studies have been performed, using acupuncturepoint-moxibustion, acupuncture, or electro-acupuncture, to correct breech presentation. In correcting breech position, acupuncture on point BL 67 is sometimes used in conjunction with heat through moxibustion, or electric stimulation<sup>15-17</sup>.

Moxibustion is the burning of a roll of specially prepared herbs containing *Artemisia vulgaris* or other *Artemisia* species ('mugwort'; the Japanese name for it is moxa) to stimulate acupuncture points without needling<sup>18,19</sup>. The temperature intensity of the moxibustion is just below the individual tolerability threshold, causing hyperaemia from local vasodilatation.

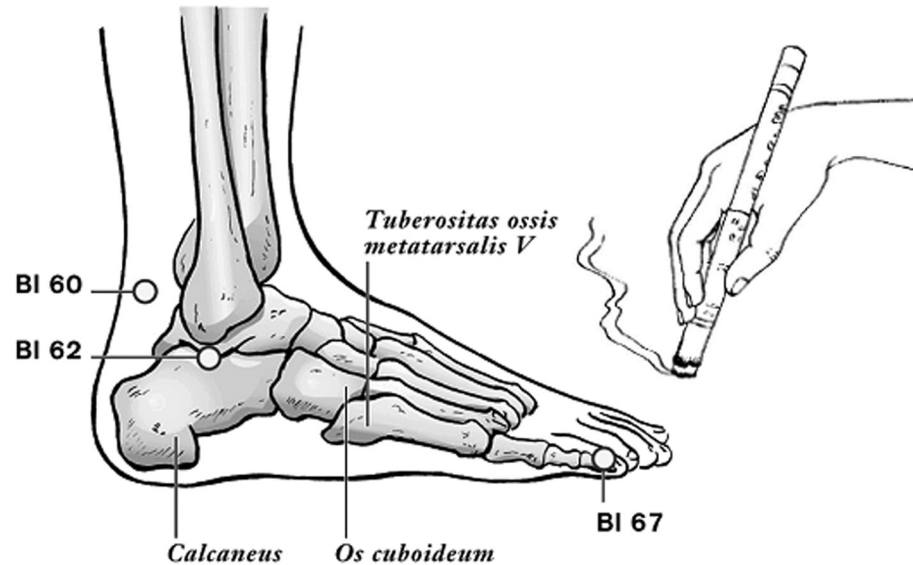
The purpose of this study was to perform a systematic review of reported studies to evaluate the effectiveness of acupuncture-type interventions on BL 67 (moxibustion, acupuncture, and electro-acupuncture) compared to expectant management to correct breech presentation.

## METHODS

### Data sources and data extraction

A literature search was performed in Medline (Pub Med), EMBASE, Cochrane Central Register of Controlled trials, AMED (Allied and Complementary Medicine), NCCAM (The National Centre for Complementary and Alternative Medicine), and Midirs (Midwifery Information Service)<sup>20</sup>. The reference lists of the literature found were searched for more articles. We contacted the original authors for further information if necessary. Key words for the search were “moxibustion AND breech”, “acupuncture AND breech”, “pregnancy AND moxibustion”. Articles were not masked for language, author or journal.<sup>21-23</sup> A study was included if the following criteria were met: (a) it was an original article; (b) published from 1980 to May 2007; (c) presenting results of an RCT or a cohort study including a control group; (d) of a traditional Chinese medicine acupuncture-type intervention of acupuncture point BL 67 in which (e) breech presentation was confirmed with ultrasound and (f) the authors reported one of the following outcome measures: position of the fetus after treatment confirmed with ultrasound, position of the baby at delivery, and/or number (and percentage) of caesarean sections. A study was excluded if sample size was not reported.

**Figure 1** Moxibustion of ZhiYin, Bladder 67.



Three authors (IvdB, BJ, and IB) independently selected and reviewed the articles and evaluated all reports for inclusion and exclusion criteria. Next, the same reviewers independently extracted the data concerning study design, patient characteristics, intervention, and outcomes. Disagreements were resolved by consensus.

### Statistical analysis of the data

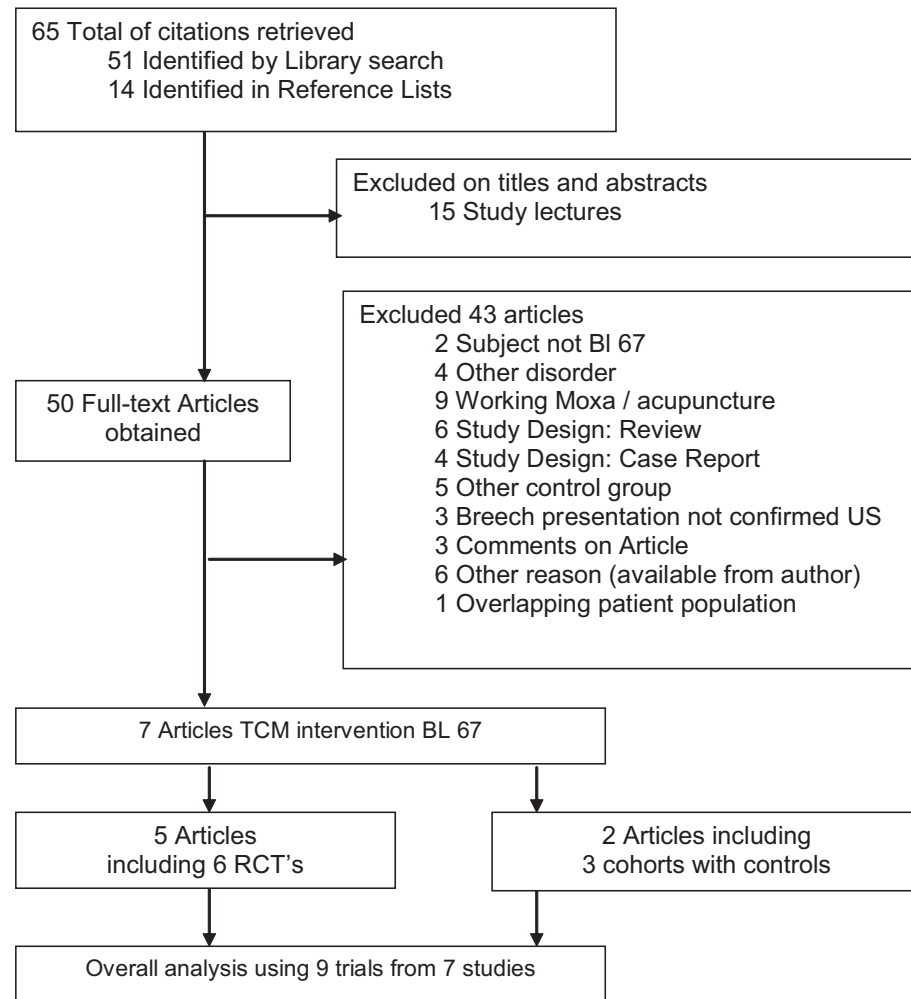
The primary outcome of our analysis was the proportion of breech presentations following the period of the acupuncture-type intervention. In addition, we assessed and explored each relevant methodological aspect individually.<sup>24</sup> We also analysed possible treatment side effects.

To detect the presence of publication bias, we constructed a funnel plot in which we plotted the sample size of the study population as a function of the natural logarithm of the odds of a fetus in breech presentation<sup>25</sup>.

The results within the intervention group and the expectant management group were tested for heterogeneity using the  $\chi^2$ -test ( $p = 0.05$ ) and the Higgins  $I^2$  test<sup>26</sup>. Random effects models take into account the variation within a study, but also variation between the various studies. Using random effects models, we pooled the proportion breech presentations following the treatment-period of the intervention groups and of the expectant management groups<sup>27</sup>.

Furthermore, we calculated the pooled OR with the 95% CI of breech presentations following the period of treatment of the intervention groups and of the expectant management groups<sup>28</sup>. The data of the RCT's and the observational cohorts with a control group were pooled separately and jointly. All analyses were performed in SAS (Proc Mixed for Windows 8.2 1999-2001, SAS Institute Inc., Cary, NC, USA) and Excel (Microsoft Windows Excel 2000 professional, Microsoft Corporation, Phoenix USA), using the formulas described by Laird and Mosteller<sup>27</sup>.

**Figure 2** Flowchart of the reviewed literature. From the initial search, a total of 65 abstracts were retrieved.



Flowchart of the reviewed literature. From the initial search, a total of 65 abstracts were retrieved. Of these 65 abstracts, 15 were study lectures<sup>12,13,34,46–57</sup>. Of the remaining 50 abstracts, the full papers were retrieved and evaluated for the additional selection criteria. The following articles were excluded: in two studies the intervention was not performed on BL 67<sup>58,59</sup>; in four studies no acupuncture-type intervention was used for other disorders<sup>60–63</sup>; nine articles were about the mechanism of Moxa<sup>18,19,33,36,64–68</sup>; six articles were reviews<sup>43,69–73</sup>; four articles were case reports<sup>51,74–76</sup>; two articles were cohort studies with controls retrospectively assessed from the Chinese literature<sup>77,78</sup>; three articles had no comparable control group.<sup>79–81</sup> In three studies the breech presentation was not confirmed with US.<sup>11,14,82</sup> Three were opinion papers<sup>83–85</sup> and six articles were excluded for other reasons.<sup>7,13,86–89</sup> Two articles reported on overlapping patient populations of which we included only the most recent study<sup>32,38</sup>.

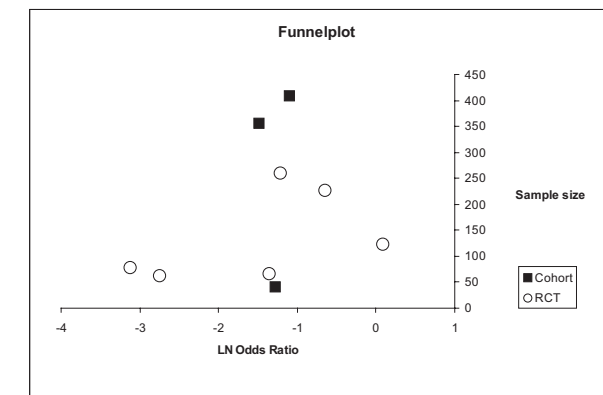
## RESULTS

### Literature search

Our search identified 65 studies, of which we excluded 15 on the basis of the abstract and 43 studies on the basis of the full text (Fig. 2). In total seven articles met the inclusion criteria and were included in our study (Table 1). Six RCT's were described in five articles<sup>15,17,29–31</sup>, that is, one paper reported on two RCT's<sup>17</sup>. In two articles the results of three cohort studies with control groups were described<sup>16,32</sup>, that is, one article reported on two patient cohorts<sup>16</sup>. The research findings from studies reported in the same source, applied the treatments in different randomly selected group of subjects and therefore we believe the independent assumption is reasonable<sup>16,17</sup>.

### Funnel plot

To detect publication bias, we constructed funnel plots (Fig. 3). The data points for the included studies are symmetrically distributed in an inverted funnel shape suggesting the absence of publication bias.



**Figure 3** Funnel plot. The funnel plot shows the number of patients included in the study versus the natural logarithm of the odds ratio of breech presentation after treatment. The data points are symmetrically distributed in an inverted funnel shape indicating that the presence of publication bias is unlikely.

### Study characteristics

The characteristics of the included studies are shown in Table 1 a and b. Six of the nine studies used moxibustion,<sup>15–17,29,30,32</sup> among which one study performed combined moxibustion with needling<sup>15</sup>. One study used acupuncture<sup>31</sup>, and two studies electroacupuncture stimulation of BL 67<sup>16,17</sup>. RCT's were computer randomised and written informed consent was obtained in all studies. In one study the evaluator was blinded to the participant's group allocation<sup>29</sup>.

**Table Ia.** Demographics of the studies included in the analysis

Study	Year	Country	Race	N intervention group	Mean age intervention group (sd)	N control group	Mean age control group (sd)	Withdrawal Intervention + Control
RCT								
Cardini, F <sup>64</sup>	2005	Italy	Caucasian	65	31	58	31	14+? ‡
Neri, I. <sup>12</sup>	2004	Italy	Caucasian	112	30.1 (3.6)	114	31.7 (14.7)	8+6
Habek, D. <sup>66</sup>	2003	Croatia	Caucasian	34	22 (3.1)	33	23 (1.3)	n/r
Cardini, F <sup>65</sup>	1998	China	Chinese	130	25.2	130	25.5	9+0
Li, Qinghua <sup>14</sup>	1996	China	Chinese	32	22-36	31	22-36	n/r
Li, Qinghua <sup>14</sup>	1996	China	Chinese	48	22-36	31	22-36	n/r
Total				421		397		
Cohort with control group								
Kanakura, Y. <sup>13</sup>	2001	Japan	Japanese	133	28.4	224	n/r	n/r
Kanakura, Y. <sup>13</sup>	2001	Japan	Japanese	191	n/r	217	n/r	n/r
Cardini, F. <sup>63</sup>	1993	Italy	Chinese	23	20-37	18	22-31	n/r
Total				347		459		
Overall				768		856		

‡ 22 % of Italian participants temporarily or definitively interrupted the treatment because of uncomfortableness due to Moxa n/r: not reported

**Table Ib.** TCM-type interventions on BL 67

Study, First author	Mean Gestational age at inclusion (weeks)	Intervention Group	Treatment time per point (min)	Treatment frequency (per day)	Treatment period (weeks)	Controls
RCT						
Cardini F <sup>64</sup>	33	Moxa	15	1	1-2	EM
Neri, I. <sup>12</sup>	33.7 a	Acupuncture + Moxa	10	2c	1-2	EM
Habek, D. <sup>66</sup>	34	Acupuncture	30	1	1-3	EM
Cardini, F <sup>65</sup>	33	Moxa	15	1-2	1-2	EM
Li, Qinghua <sup>14</sup>	28*	Moxa	20	n/r	1-6 c	EM
Li, Qinghua <sup>14</sup>	28*	Electro-acupuncture	30	n/r	1-6 c	EM
Cohort with control group						
Kanakura, Y. <sup>13</sup>	28 *	Moxa d	5	1	until correction	EM
Kanakura, Y. <sup>13</sup>	28 *	Electro-acupuncture	5	n/r	n/r	EM
Cardini, F. <sup>63</sup>	33	Moxa	15	1	5-40 days	EM/Æ

EP Expectant Policy

n/r: Not reported

a SD 0.7

\* Minimal gestational age

b Per week

c Sessions

d BL 67 used in combination with 5 other acupuncture points

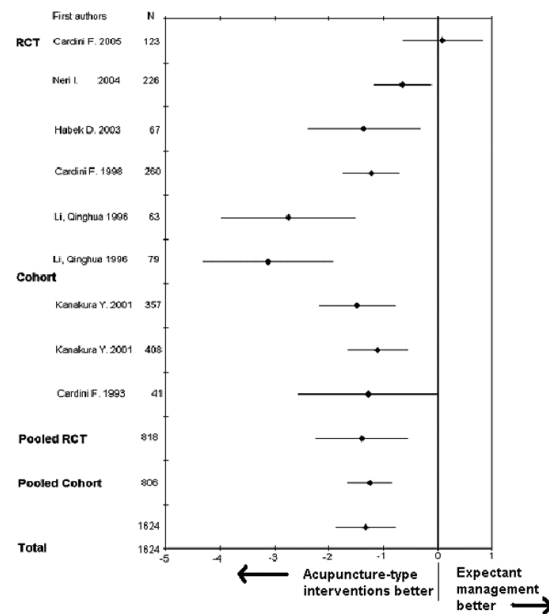
Æ Retrospective controls



Heterogeneity was found between all the studies ( $\chi^2 = 9.3$  ( $p$ -value = 0.001); the estimated natural logarithm of the odds ratio (ln OR) and the approximate 95% confidence intervals (CI) varied between the nine studies (Fig. 4). The Higgins  $I^2$  value (=96.2%) is close to 100% implies that there is high heterogeneity across the studies. Therefore, we use a random-effects approach to take into account this variability<sup>26</sup>. The random-effects model was used to pool the outcomes<sup>27</sup>.

### Harms of the interventions

No significant harmful effects of moxibustion on women or their infants were reported during or immediately after performing the treatment; that is, no signs of fetal distress, preterm uterine contractions or maternal cardiovascular changes occurred<sup>33</sup>. In the two RCT's of Cardini, however, cases of preterm premature rupture of the membrane (PPROM) were reported in the intervention groups<sup>29,30</sup>. In the Italian study, two cases of preterm deliveries were described, one certain, due to PPRM, one suspected which occurred at 34 weeks of gestation, and no PPRM was recorded in the control group<sup>29</sup>. After delivery of the described cases by caesarean section, there were no consequences for the neonates described. In the Chinese study, no adverse events occurred during treat-



**Figure 4** Odds ratio's (log scale) and 95% confidence intervals of breech presentations. Odds ratio's (log scale) and 95% confidence intervals of breech presentations following the period of treatment of the intervention groups and of the expectative policy groups for acupuncture-type intervention for individual studies and the pooled results.  $N$  = total of subjects. The plot shows substantial heterogeneity in the estimated effects among the studies.

ment. Preterm rupture of the membrane (PROM) occurred in three cases at 37 weeks gestation, which was at least 2 weeks after completion of treatment<sup>30</sup>.

In some studies withdrawal from the study was reported<sup>29,30,34</sup>. The main reported reasons were the aggravation of respiratory symptoms and un-comfortableness on exposure to the moxa smoke. Other reasons were uterine contractility, mild hypertension, and reluctance to comply<sup>29,30,34</sup>.

### Benefits of the interventions

Eight of the nine studies demonstrated that treatment on BL 67 was effective in correcting breech presentation whereas in one study poor compliance of the clients led to interruption of the study and no effect could be demonstrated<sup>29</sup> (Table 2). In the pooled RCT's, 421 women were included in the intervention group and 397 women in the expectant management (control) group (Table 2). The pooled RCT's demonstrated a significant effect of the intervention: the proportion of breech presentations in the intervention group was 34% versus 66% in the control group (OR 0.25, 95% CI: 0.11-0.58) (Table 2, Fig. 4).

In the pooled controlled cohort series, the proportion of breech presentations in the intervention group was 15% ( $n = 347$ ) versus 36% in the control group ( $n = 459$ ) (OR 0.29, 95% CI: 0.19-0.43) (Table 2, Fig. 4). Combining all studies, the proportion of breech presentations in the intervention group was 28% ( $n = 768$ ) versus 56% in the control group ( $n = 856$ ) (OR 0.27, 95% CI: 0.15-0.46) (Table 2, Fig. 4).

## DISCUSSION

In this systematic review, we found a beneficial effect of acupuncture-type interventions stimulating BL 67 to induce a version to cephalic presentation compared to expectant management. Whereas the effect was more pronounced absolutely in the RCT's, the effect was more pronounced in a relative sense in the cohort studies. In the cohort series, the percentage of breech presentations was halved with intervention, but this was not statistically significant, which may have been due to the limited sample size. The pooled result of the RCT's and that of all studies combined demonstrated a

Table 2. Outcomes of the individual studies and pooled outcomes

Reference	n intervention group	N in breech during follow-up	Percentage Breech	n control group	N in breech during followup	Percentage Breech	OR Breech presentation
Cardini, F. <sup>64</sup>	65	43	66.2	58	37	63.8	1.09
Neri, I. <sup>12</sup>	112	52	46.4	114	71	62.3	0.52
Habek, D. <sup>66</sup>	34	8	23.6	33	18	54.6	0.26
Cardini, F. <sup>65</sup>	130	32	24.4	130	68	52.3	0.29
Li, Qinghua <sup>14</sup>	32	8	25.0	31	26	83.9	0.06
Li, Qinghua <sup>14</sup>	48	9	18.7	31	26	83.9	0.04
<b>Pooled results RCTs (CI)</b>	<b>421</b>	<b>152</b>	<b>34% (20%, 49%)</b>	<b>397</b>	<b>197</b>	<b>66% (55%, 77%)</b>	<b>0.25 (0.11, 0.58)</b>
Kanakura, Y. <sup>13</sup>	133	10	7.5	224	59	26.3	0.23
Kanakura, Y. <sup>13</sup>	191	21	10.5	217	57	26.1	0.33
Cardini, F. <sup>63</sup>	23	7	30.4	18	11	61.1	0.28
<b>Pooled Results Cohort studies (CI)</b>	<b>347</b>	<b>38</b>	<b>15% (1%, 28%)</b>	<b>459</b>	<b>127</b>	<b>36% (14%, 58%)</b>	<b>0.29 (0.19, 0.43)</b>
<b>Pooled results Combined studies (CI)</b>	<b>768</b>	<b>190</b>	<b>28% (16%, 40%)</b>	<b>856</b>	<b>324</b>	<b>56% (43%, 70%)</b>	<b>0.27 (0.15, 0.46)</b>

clinically and statistically significant reduction in breech presentations.

As a rule, cohort series generally demonstrate a larger effect than RCT's and are more likely to reach statistical significance. In contrast, we found that the pooled RCT's demonstrated a larger absolute effect than the cohort studies and the effect was significant in the pooled RCT's whereas in the pooled cohort studies it was not. A possible explanation for these findings is that the gestational age at the time of inclusion in two cohort studies was lower than in the RCT's<sup>16</sup>. Prior to 32 weeks gestational age, spontaneous version occurs more often than after 32 weeks (11.5% versus 6.3% to a nadir of 1.7% after 40 weeks)<sup>1,13,32</sup>. This will have an effect in both the intervention group and the expectant management group resulting in lower proportions of breech presentation and a smaller absolute effect of the intervention in the cohort studies compared to the RCT's. It has been suggested that also patient age and condition, female babies, fetal motor activity and room temperature during treatment could play a role in the effectiveness of acupuncture-type interventions on correcting breech presentations<sup>14,35</sup>. Overall there are few well designed studies exploring the role of these covariates in relation to different treatment designs. The decision was made not to conduct a meta-analysis including these covariates due to the significant differences in the intervention type. Further studies are necessary to establish the related results.

The mechanism of stimulation of BL 67 has, in part, been scientifically investigated. One study of the morphological basis and relationship between BL 67 and the viscera showed that seven segments (L2-S1) of the uterus and the sensory innervation of BL 67 overlap<sup>36</sup>. Other authors suggested that the stimulation of BL 67 increases cortico-adrenal secretion, placental estrogens, and changes in prostaglandin levels, leading to raised basal tone of the uterus and enhanced movement of the fetus, thus making version more likely<sup>11,16,33,37-40</sup>. The explanation that version of the fetus would be purely based on a reflex action of moxibustion mediated by a dermatome must be rejected, because stimulation of BL 67 performed in cases of intrauterine fetal death failed to produce version<sup>38</sup>. According to the acupuncture point of view, one of the functions of BL 67 is to stimulate the activity of the fetus, which may be an important mechanism to induce spontaneous version. Furthermore, it seems likely that the technique may be more successful in complete breech presentation than in frank or footling breech presentation<sup>29,41</sup>. In this systematic review data from nine studies were extracted, reviewed,

compared, and pooled odds ratios were reported. Many systematic reviews only consider randomised controlled trials (RCT's), which are generally considered the state-of-the-art study design for evaluation of interventions. Linde, however, suggested that non-randomised studies might also be useful in a systematic review to get a more comprehensive overview of current practice and to inform future research<sup>42</sup>. Therefore, in our literature search, we also considered non-randomised studies.

A limitation of our systematic review, as with other reviews, was that the possibility of publication bias cannot be ruled out, even though our funnel plot did not demonstrate the presence of publication bias. We searched different sources to identify all RCT's and cohort studies with controls of TCM interventions on BL 67 for correction of breech presentation, but were not able to retrieve any unpublished studies. Although the use of acupuncture is widespread in China and Russia, our literature search retrieved only four eligible trials from China and none from Russia. Databases only partially cover literature from these countries and it is possible that unidentified eligible trials from these countries exist.

Another limitation of our study was that the sample sizes of RCTs included were relatively small and details of the study design and certain outcomes were sometimes not reported. For example, in three RCT's, the caesarean section rate was described<sup>15,30,31</sup>. Some consider caesarean section as an important outcome of the treatment effect. However it should be noted that the number of caesarean sections performed is not only determined by the effect of treatment but also by other factors such as many other medical indications as well as the women's own preferences. In the included studies elective caesarean deliveries for breech presentations were not studied.

Furthermore, among the included studies, a variety of acupuncture-type interventions (moxibustion, moxibustion combined with acupuncture, acupuncture alone, and electro-acupuncture) and protocols were used. Although of the included studies the most commonly used method was moxibustion, with a protocol of once a day for 15-20 min for as long as 1-2 weeks. The effect of these different interventions is unknown and beyond the scope of the current review. A Cochrane review on this topic, however, also concluded that there was no consensus in the literature with respect to the best regimen<sup>43</sup>.

In contrast to our study, the Cochrane review focused on the treatment of BL 67 with acumoxa only and concluded that moxibustion may help to correct breech presentation but that the number of studies was too small to demonstrate effectiveness with statistical significance.

Other limitations of our study are the poorly defined and reported characteristics of the women and fetuses, and outcomes of treatment in the original studies after treatment and at term and restricted our ability to adjust for differences in case mix and outcome measures (Table 1).

With the available data it was impossible to find a significant relation between acupuncture-type interventions of BL 67 and preterm birth due to PPRM. To assess the frequency of the possible relation, further studies are required.

Nevertheless, not only the method of stimulation and different protocols, but also ethnic, cultural and educational differences could account for the different results reported in the different studies.

Another limitation is that we could not adjust for parity because parity was often not reported, two studies were performed with only primigravid women<sup>29,30</sup>. Among the included studies that considered parity, only one study demonstrated a significant difference between primi- and multiparae<sup>15</sup>. The success rate of version to cephalic presentation may be related to the fact that the uterus of a multipara already reached the maximum length and so there is more room for version of the fetus. From the 37th week, spontaneously movement into cephalic presentation is not longer likely to occur, in either primiparae or multiparae<sup>44</sup>. In one study, parity was even found to be the only significant factor in predicting the success of external cephalic version<sup>45</sup>.

Finally, the primary outcome measures of interest in RCTs that evaluate acupuncture-type interventions for correction of breech presentation would have been fetal presentation at the time of delivery, preferably adjusted for covariates. Secondary outcome measures of interest would be mode of delivery and neonatal outcome, including safety, morbidity and mortality. Relevant covariates would be parity, type of breech presentation, active-fetal-movements, location of the placenta, the amount of amniotic fluid, educational level, culturally defined expectations of therapy, previous caesarean sections, reason for performing previous caesarean section, and the women's viewpoint with respect to vaginal versus caesarean delivery.

In addition, the ideal study design may be placebocontrolled RCT, but due to the relative contraindication to the use of moxibustion during pregnancy in other locations than BL 67 it is not feasible to use a placebo moxa treatment. Besides that, a placebo intervention would quickly be identifiable as placebo by the patient and her partner through the informed consent procedure and through information about moxibustion on the Internet.

Based on the results of our study, the effect of using acupuncture-type interventions on BL 67 to correct breech presentation seems promising. Our results, however, are influenced by the variety of the included studies. Therefore, before making this adjuvant treatment to standard Western healthcare, we recommend to conduct a largescale RCT in which moxibustion is compared to expectant management. We recommend moxibustion, as this method is inexpensive, readily available, safe, client-friendly, and can be performed at home by the partner of the pregnant woman. In addition, more characteristics of the participants, such as parity, fetal position, both after treatment and at time of delivery, maternal and fetal complications, information of external cephalic version and its outcome, and the number of caesarean sections with the reasons for performing them, should be monitored. Also, womens preferences, the acceptance of the smell and warmth of the moxibustion treatment, quality of life of the women, and healthcare and non-healthcare costs should be assessed.

## CONCLUSIONS

Our systematic review of the current literature shows a beneficial effect of using acupuncture-type interventions on BL 67 to induce correction of a breech presentation compared to expectant management. Our results, however, are influenced by the existing differences in design of the current studies and further RCT's of improved quality are necessary to adequately answer this question.

## CONFLICT OF INTEREST STATEMENT

We have no conflict of interest to declare. All authors and researchers involved state to be independent from the funding organisation (NVA). The authors' work was independent of the funding organisation. The funding organisation had no involvement in the study design, data collection and analysis, writing of the manuscript, or in the decision to submit this article for publication.

## STATEMENTS

Authorship contribution: The authors assure that all authors included in this paper fulfil the criteria of authorship and that there is no one else who fulfils the criteria but who has not been included as an author. Guarantor: The corresponding author, Ineke van den Berg, states to accept full responsibility for the work and conduct of the study, to have had full access to the data and to have controlled the decision to publish.

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## Correction of nonvertex presentation with moxibustion

### TO THE EDITORS

With great interest we read the article by Vas et al.<sup>1</sup> This systematic review and meta-analysis exhaustively discusses 7 studies comparing moxibustion and other methods for correction of nonvertex presentation. The major conclusion is that with regard to the correction of nonvertex presentation, there is a beneficial effect of moxibustion applied at the acupuncture point BL 67.

However, this study has some limitations. The studies included in the review use a variety of control groups. The treatment in some of the control groups is only observational, so women in these groups get no treatment at all,<sup>2-4</sup> while women in other control groups get interventions such as postural inducement of version<sup>5-7</sup> and acupuncture on BL 67.<sup>8</sup> Besides, the treatment groups in the studies included in the review also use a variety of treatments. Some of the treatment groups only get moxibustion,<sup>2,4,7,8</sup> while other treatment groups get acupuncture<sup>3</sup> or knee-to-chest posture next to moxibustion.<sup>5,6</sup>

It would have been more justified if the 2 studies with observational control groups vs moxibustion alone in the treatment groups were separated from the other studies. From these other studies, it would be justified to separate the studies in which moxibustion plus knee-to-chest posture is compared to only knee-to-chest posture. In this way, the results of the moxibustion treatment would have been more interpretable for clinical use.

In March 2008, we published a systematic review of studies assessing the effectiveness of acupuncture-type interventions (moxibustion, acupuncture, or electro-acupuncture) on acupuncture point BL 67 to correct breech presentation compared to expectant management, based on controlled trials.<sup>9</sup> Several of the 9 studies reviewed overlap with those reviewed by Vas et al.<sup>1</sup> Unfortunately, Vas et al.<sup>1</sup> were obviously unable to make a comparison with our review. By design we included only studies that used a control group without any intervention. We concluded that the current literature shows a beneficial effect of using acupuncture-type interventions on BL 67, including moxibustion, to induce correction of a breech presentation compared to expectant management.

Ineke van den Berg, MSc Departments of Epidemiology and Radiology Erasmus University Medical Center PO Box 2040 3000 CA Rotterdam, The Netherlands [ineke.vandenberg@erasmusmc.nl](mailto:ineke.vandenberg@erasmusmc.nl)

Lidia R. Arends, PhD Department of Biostatistics Erasmus University Medical Center Rotterdam, The Netherlands

Johannes J. Duvekot, MD, PhD  
Department of Obstetrics and Gynecology Erasmus Medical Center  
Academic Hospital Rotterdam  
Rotterdam, The Netherlands

### REPLY DECLINED

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Chapter **7**

**Cost-effectiveness of Breech  
Version by Acumoxa for women  
with a breech foetus at 33 weeks  
gestation: a modelling approach**

Ineke van den Berg  
Guido C. Kaandorp  
Johanna L. Bosch  
Johannes J. Duvekot  
Lidia R. Arends  
M.G. Myriam Hunink

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## SUMMARY

**Objectives** To assess, using a modelling approach, the effectiveness and costs of breech version with acupuncture-type interventions on BL67 (BVA-T), including moxibustion, compared to expectant management for women with a foetal breech presentation at 33 weeks gestation.

**Design** A decision tree was developed to predict the number of caesarean sections prevented by BVA-T compared to expectant management to rectify breech presentation. The model accounted for external cephalic versions (ECV), treatment compliance, and costs for 10,000 simulated breech presentations at 33 weeks gestational age. Event rates were taken from Dutch population data and the international literature, and the relative effectiveness of BVAT was based on a specific meta-analysis. Sensitivity analyses were conducted to evaluate the robustness of the results.

**Main outcome measures** We calculated percentages of breech presentations at term, caesarean sections, and costs from the third-party payer perspective. Odds ratios (OR) and cost differences of BVA-T versus expectant management were calculated. (Probabilistic) sensitivity analysis and expected value of perfect information analysis were performed.

**Results** The simulated outcomes demonstrated 32% breech presentations after BVA-T versus 53% with expectant management (OR 0.61, 95% CI 0.43, 0.83). The percentage caesarean section was 37% after BVA-T versus 50% with expectant management (OR 0.73, 95% CI 0.59, 0.88). The mean cost-savings per woman was € 451 (95% CI € 109, € 775;  $p = 0.005$ ) using Moxibustion. Sensitivity analysis showed that if 16% or more of women offered moxibustion complied, it was more effective and less costly than expectant management. To prevent one caesarean section, 7 women had to use BVA-T. The expected value of perfect information from further research was € 0.32 per woman.

**Conclusions** The results suggest that offering BVA-T to women with a breech foetus at 33 weeks gestation reduces the number of breech presentations at term, thus reducing the number of caesarean sections, and is cost-effective compared to expectant management, including external cephalic version.

## INTRODUCTION

In pregnancies at term, about 3-5% of singleton fetuses present in breech position<sup>1</sup>. Caesarean section has become common practice for term breech deliveries in many Western countries<sup>2-6</sup>, but is not without disadvantages. Apart from the 1.29 relative risk (95% CI 1.03-1.61) of immediate severe maternal morbidity<sup>2,7</sup>, there is the risk of adverse effects on subsequent pregnancies<sup>4,8-11</sup>. Potential complications include deep-vein thrombosis, pulmonary thrombo-embolism, need for transfusion, puerperal infection, postpartum hemorrhage, neonatal respiratory distress, maternal urinary tract infection, wound infection, and scar dehiscence or uterine rupture during subsequent labor. Moreover, a higher number of caesarean sections could entail higher societal costs. Therefore, viewed from various perspectives, it would seem important to find ways to correct breech presentation before delivery.

One option is a procedure called external cephalic version (ECV), recommended by the American College of Obstetricians and Gynaecologists (ACOG) and the British Royal College of Obstetricians and Gynaecologists (RCOG)<sup>12,13</sup>. This procedure is successful in 50 to 60% of cases and is usually performed by a gynaecologist starting at 36 weeks gestation<sup>14,15</sup>. On the other hand, serious complications, such as perinatal death, need for emergency caesarean deliveries and a spontaneous reversion rate of 3% have been reported<sup>15-19</sup>. In addition, ECVs generate costs.

Another, non-invasive, method to correct breech presentation comes from traditional Chinese medicine. Named Breech Version Acumoxa, the moxibustion of acupuncturepoint Zhiyin, Bladder 67 (BL67, located beside the outer proximal corner of the toenail of the fifth toe), was first reported in 1980 as a safe and non-invasive way to correct breech presentation<sup>20</sup>. Since this Chinese study, various controlled studies in other countries have evaluated the merits of breech version by acupuncture-type interventions on BL 67 (BVA-T) including acupuncture-point-moxibustion, acupuncture, or electro-acupuncture<sup>21-26</sup>. Moxibustion is the burning of a roll of herbs (*Artemisia Vulgaris* = Moxa) to stimulate acupuncture points without needle insertion. The sticks are readily available, safe and user-friendly and can be applied by anyone following skilled instruction<sup>27-29</sup>.

A systematic review and meta-analysis of studies reporting the results of randomized controlled trials (RCTs) on acupuncture-type interventions on BL 67 versus expectant management showed that the pooled proportion of

breech presentations was 34% (95% CI: 20-49%) in the treatment group versus 66% (95% CI: 55-77%) in the control group<sup>30</sup>. In this meta-analysis, three of the six studies used moxibustion, the other three used acupuncture, electro-acupuncture, and a mixture of moxibustion and acupuncture on BL 67.

In general, there is growing willingness of hospital departments and patients to adopt complementary care, provided it is safe<sup>31-33</sup>. More specifically in obstetrics, health-care providers are recognizing the favourable economic impact of low-cost, complementary therapies<sup>34</sup>. However, to decide whether BVA-T should be offered alongside the standard care of expectant management to correct breech presentation policymakers need more detailed information.

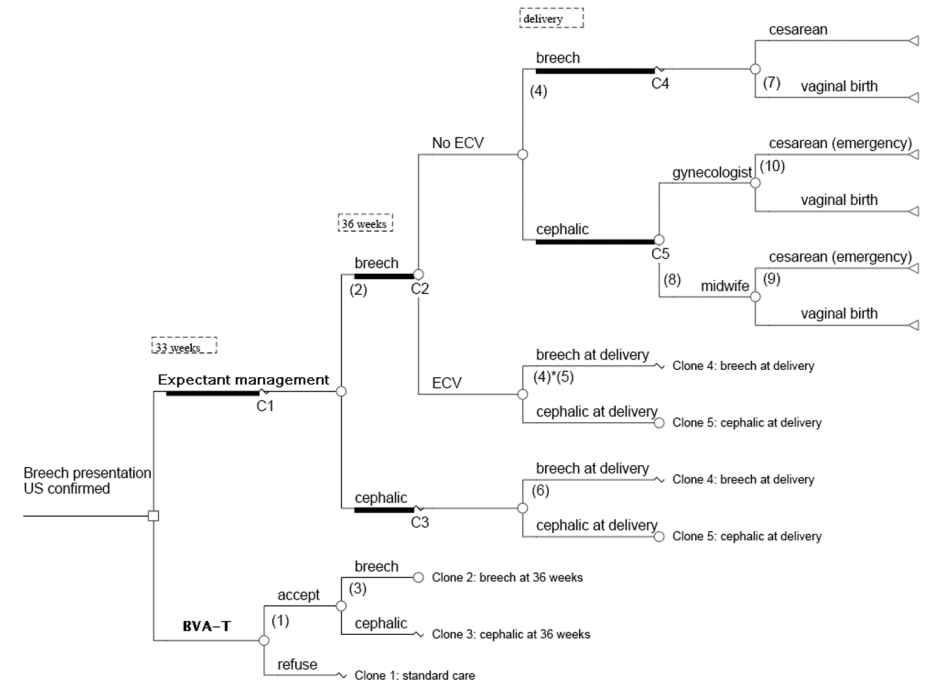
Our aim was to generate information by a decision-analytic approach about the projected effectiveness and costs of BVA-T compared with expected management including associated procedures such as external cephalic version, in order to reverse breech presentation after the 33rd-week gestation and reduce the number of caesarean sections at term.

## DESIGN AND METHODS

### Model structure

A decision tree was constructed to assess the effectiveness and costs of two strategies – “BVA-T” and “expectant management” (EM) - to facilitate spontaneous cephalic version of a foetus in breech position at 33 weeks gestation<sup>35,36</sup> (Fig. 1). Box 1 explains the terminology related to decision models in general. Outcome measures for effectiveness were percentage of breech presentations at term/delivery and percentage of caesarean sections. Costs were defined as third-party payer costs.

The model started at 33 weeks gestation and followed the time path until 1 week after delivery. At the starting point, breech presentation had been confirmed with ultrasonograph (US). In both strategies, a second US was performed at 36 weeks gestation. The model took into account events such as refusing BVA-T, lack of compliance to BVA-T, and spontaneous version. Both strategies included the option to have an ECV performed by a gynaecologist from 36 weeks gestation. Furthermore, in both strategies all births



**Figure 1** Decision tree for the decision of whether to add BVA-T to rectify breech presentation in generally healthy 33 weeks pregnant women with a breech baby. This decision model was also developed to predict the number of caesarean sections prevented by comparing BVA-T with expectant management (EM) to rectify breech presentation, including treatment compliance, and costs and associated event as external cephalic version (ECV). Shown is the generic framework of the model. The square node at the far left symbolizes the choice between BVA-T and EM. The tree is fully displayed only for the EM arm, but the BVA-T arm has the same detail. Generally healthy 33 weeks pregnant women with a breech baby cycle through the tree and are at risk for breech presentation at term and the risk of caesarean section at delivery. The square indicates the choice between BVA-T and EM, circles represent potential chance consequences, and triangles signify six different outcomes. The decision tree included five clones, after which it followed the branch indicated with C1 till C5. The numbers between brackets indicate the variables with their probabilities (Table 1).

took place in hospital, assisted by a midwife or gynaecologist depending on the mother’s and foetus’s health status. BVA-T implied two instructional visits to an acupuncturist at 33 and 34 weeks gestation, with daily treatments performed at home, applied by the partner, during the intervening week. EM implied that the midwife would be in a “wait and see mode” until 36 weeks gestation. The model was consistent with the recommendation of the Dutch obstetric organization that healthy pregnant women are cared

**Box 1.** Explanation of terminology related to decision models in general

**Decision analysis** is a mathematical approach to making decisions based on weighing risks and benefits in an explicit quantitative manner.

**Decision trees** are visual representations of decision analytical models which depict all possible choices or strategies (at the **decision node**, depicted with a square), the consequences of these choices (at **chance nodes**, depicted with circles), and the outcomes of these consequences (at the **terminal nodes**, depicted with triangles or rectangles).

**Cost-effectiveness analysis** is an assessment of both the costs and effectiveness associated with different management strategies for a health-care problem.

**Perspective** is the viewpoint taken in performing the analysis which can be the patient, the physician, the department, the hospital, the third-party payer, the health-care system, or society.

**Variables** are the input parameters in the model that together determine the optimal decision, e.g. effectiveness of treatment, costs of treatment.

for by well-trained midwives whereas women with maternal and/or foetal complications are referred to a gynaecologist. Breech presentation at 36 weeks gestation is a reason for referral, in which case responsibility of care shifts to the gynaecologist. The decision model was constructed in TreeAge Pro 2006 (release 1.2, TreeAge Software, Inc. Williamstown, USA).

## INPUT PARAMETERS

### Clinical effectiveness

Box 2 explains the terminology related to effectiveness. Table 1 lists the mean probabilities, 95% confidence intervals, and distributions of the vari-

**Table 1.** Overview of all variables included in the model with their references. The numbers before the variables correspond with the numbers after the chance nodes in Figure 1.

Variable	Reference	Mean (prob.)	95% CI	Distribution
(1) Acceptance Moxa	Cardini F., et al.	0.84	(0.77,0.89)	Beta(123, 24)
(2) Stay breech between week 33-36 SC	van den Berg I., et al.*	0.66	(0.54,0.77)	Beta(45.38, 23.48)
(3) Stay breech between week 33-36 Moxa	van den Berg I., et al.*	0.34	(0.21,0.5)	Beta(13.73, 26.22)
(4) Stay breech between week 36- + SC	Hofmeyr G.J., et al. <sup>o</sup>	0.80	(0.74,0.85)	Beta(175, 44)
(5) RR stay breech between week 36- + Moxa	Hofmeyr G.J., et al. <sup>†</sup>	0.38	(0.18,0.8)	Log-Normal(-1.31, 0.83)
(6) Spontaneous breech at term	Janssen P.A., et al. <sup>‡</sup>	0.01	(0.00,0.02)	Beta(7, 855)
(7) Vaginal breech delivery	Rietberg C.C.Th., et al. <sup>‡</sup>	0.20	(0.19,0.21)	Beta(2835, 11423)
(8) Cephalic delivery by midwife (hospital)	Janssen P.A., et al.	0.57	(0.54,0.59)	Beta(743, 571)
(9) Emergency cephalic caesarean by midwife (hospital)	Janssen P.A., et al.	0.18	(0.15,0.21)	Beta(135, 608)
(10) Emergency cephalic caesarean by gynecologist	Janssen P.A., et al.	0.12	(0.09,0.15)	Beta(68, 503)
(11) Emergency cephalic caesarean by midwife (home)	Janssen P.A., et al.	0.06	(0.05,0.08)	Beta(55, 807)
(12) Maternal factors and the probability of a planned home birth	Anthony S., et al. <sup>§</sup>	1/3	home births	

\* Pooled result of RCT's

<sup>o</sup> Cochrane Database Systematic Review

<sup>§</sup> Only used in sensitivity analysis for homebirth in the Netherlands

<sup>‡</sup> Confirmed by data from the Dutch Perinatal Database

ables entered into the model. The data were retrieved from a PubMed literature search restricted to English-language reports, and confirmed by data from the Dutch Perinatal Database and from expert opinions. The probabilities of included events and interventions were based on clinical practice in maternal and neonatal maternity care in the Netherlands<sup>4,37-43</sup>. The probability that a woman would accept BVA-T and the probability of persistent breech presentation between weeks 33 and 36 following BVA-T or EM (Table 1) were retrieved from a systematic review and meta-analysis<sup>30</sup>.

**Box 2.** Explanation of terminology related to effectiveness

**Effectiveness** is the expected benefit of a treatment.

The **odds ratio (OR)** is a measure of association of exposure and outcome (event) and equals the odds of risk in the exposed group divided by the odds of risk in the control group. The OR equals the cross product in a 2x2 table of exposure vs outcome. In the context of treatment the OR is a measure of the effectiveness of the treatment and equals the odds of the risk of the outcome in the treated group divided by the odds of the risk of the outcome in the control group. An  $OR < 1$  indicates an effective treatment,  $OR = 1$  an ineffective treatment, and  $OR > 1$  a harmful treatment.

The **risk difference (RD)** is a measure of association of exposure and outcome (event) and equals the risk in the exposed group minus the risk in the control group. In the context of treatment the RD is a measure of the effectiveness of the treatment and equals the risk of the outcome in the treated group minus the risk of the outcome in the control group. A  $RD < 0$  indicates an effective treatment,  $RD = 0$  an ineffective treatment, and  $RD > 0$  a harmful treatment.

The **number-needed-to-treat (NNT)** is the number of patients that need to be treated to avoid one event in a defined time period and is the inverse of the absolute risk reduction. In formula form:  $NNT = 1 / R$

## COSTS

Box 3 explains the terminology related to costs. Table 2 shows details of the cost items. Costs were assessed according to Dutch guidelines and from a third-party payer perspective. All costs related to the diagnosis and treatments of breech presentation were included<sup>44-46</sup>. In addition, both strategies included the costs of prenatal and postnatal care for 8 days after delivery, care provided by midwives and auxiliary maternity care.

Direct costs were assessed for BVA-T, ECV, caesarean section, breech vaginal birth, cephalic vaginal birth (gynaecologist) and cephalic vaginal birth (midwife).

**Box 3.** Explanation of terminology related to costs

**Direct health-care costs** are costs associated with medical procedures, hospital admissions, outpatient visits, medication, therapeutic interventions, patient care, and overhead.

**Overhead costs** are costs for the building and administration.

**Indirect health-care costs** are future costs and costs induced by the chosen strategy.

In-hospital costs were retrieved from Diagnosis-Treatment-Combinations (DTCs) and from the financial department of the Bronovo Hospital in the Hague, which is a regional hospital, the type of institution where babies in the Netherlands are usually delivered. DTCs come with fixed prices for treatment of patients with specific diagnoses and cover the complete process from the first specialist consultation to the final outpatient visit<sup>47</sup>. The DTCs applicable here do not differentiate between the different types of caesarean sections, but rather give weighted averages. Out-of-hospital costs were retrieved from the Dutch Association of Acupuncture (NVA), the Royal Dutch Organization of Midwives (KNOV), and "Maatzorg Pregnancy and Baby Care" - an organization specialized in postnatal care at home. Indirect costs and costs of subsequent pregnancies were not taken into account. Costs are reported in 2006 Euros.



## Data analysis

Box 4 explains the terminology related to decision models in general. Two main analyses were performed, namely without (0%) and with (100%) implementation of ECV. We calculated proportions of breech presentations at term and caesarean sections, and third-party payer costs for each strategy.

### Box 4. Explanation of terminology related to analyzing decision models

A **dominant strategy** is a strategy that is less expensive and more effective than the alternative strategy and is thus superior to the alternative. If dominance exists, the cost-effectiveness ratio is meaningless.

The **incremental cost-effectiveness ratio** is the incremental cost divided by the gain in effectiveness compared to the next best strategy and should be calculated in the setting of non-dominance to determine whether more money is justified by the gain in effect.

**Sensitivity analysis** is a "what-if" analysis. By varying the value of variables in the decision model we can explore the effect on the outcome and evaluate whether alternative assumptions would change the decision.

In **probabilistic sensitivity analysis** all variable values are modelled with distributions instead of deterministic values. Variable values are picked at random from the distributions for each variable and the outcomes are calculated. This is repeated multiple (e.g. 10,000) times which yields distributions of the outcomes and from which we can determine the probability that one strategy is preferred over another.

**Value of information analysis** determines the potential benefit of further research.

**Expected value of perfect information (EVPI)** is the expected incremental benefit of the optimal strategy based on accurate estimates of all the variables should these become available through further research compared to the benefit of the optimal strategy based on current information.

**Table 2.** The included costs per procedure in the decision tree.

	Description	Source	Cost (€)
Interventions	Moxa	NVA, KNOV, NatuurApotheek®	158.50
	ECV	DTC	885.45
Prenatal	Gynecologist	DTC	518.26
	Midwife	KNOV	343.00
Delivery	Caesarean section	DTC + overhead regional hospital	5,075.67
	Assisted breech vaginal birth	DTC + overhead regional hospital	1,916.49
	Assisted cephalic vaginal birth (gynecologist)	DTC + overhead regional hospital	1,827.93
	Assisted cephalic vaginal birth (midwife)	DTC	721.50
Postnatal	Caesarean	DTC/KNOV, www.progeria.nl	637.20
	Vaginal birth	KNOV, www.progeria.nl	1,564.70

Next, we calculated the odds ratios (OR) of BVAT versus EM for the proportion of breech presentation and caesarean sections and we calculated the difference in third-party payer costs between the strategies.

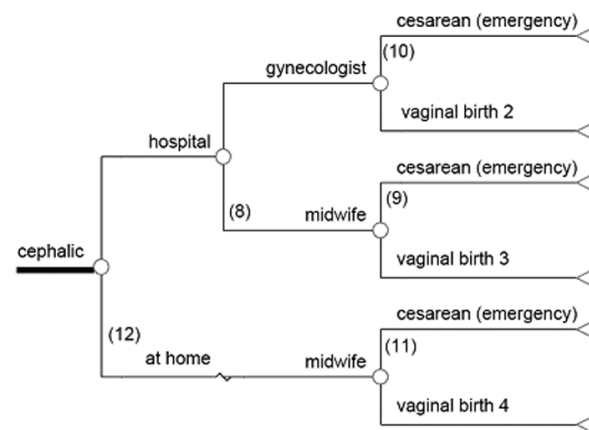
We took the inverse of the absolute risk difference (RD) to calculate the number of women - needed-to-treat with BVA-T to prevent one caesarean section.

### Sensitivity analysis

Our initial analyses were based on 100% hospital births, which were assisted by a gynaecologist or midwife. Cultural differences in birth settings, however, do exist. For example, in the Netherlands, many home-births take place and midwives provide basic care to pregnant women and serve as an arbitrator for the admission of more complex pregnancies to gynaecologists<sup>48</sup>. To specifically evaluate the effect of these cultural differences, we performed sensitivity analyses in which we extended our original decision tree and added the proportions of home-births (i.e., 33.3%) versus hospital-births (66.7%) (Fig. 2).

In our initial analyses, breech presentation at 33 weeks gestation was always confirmed

by US. In practice, however, this is not always done. In additional sensitivity analyses, therefore, we adopted a 20 to 100% range of confirmed breech presentations rather than 100%. In addition, the acceptance rate of BVA-T was varied from 0 to 100% to demonstrate the impact on total costs.



**Figure 2** Extension of the decision tree in which home-births were included. The numbers between brackets indicate the probabilities corresponding with Table 1.

### Probabilistic sensitivity analysis and value of information analysis

All probabilities were modelled with beta or lognormal distributions (Table 1). Probabilistic sensitivity analysis, using 10,000 second-order Monte Carlo simulations, was performed and provided the 95% confidence intervals around the estimates. In addition, this analysis provided the probability that EM rather than BVA-T would be the optimal strategy.

Value of information analysis was performed to determine the potential benefit of further research. We calculated the expected value of perfect information (EVPI), which is the expected incremental benefit of the optimal strategy based on exact accurate estimates of all the variables compared to the benefit of the optimal strategy based on current information. Since obtaining exact accurate estimates of parameter values is impossible (it needs a study with an infinite sample size evaluating all parameters), EVPI is the upper limit of the expected benefit of further research<sup>49-51</sup>.

## RESULTS

Table 3 shows the main simulated outcomes of the initial analyses. Without the option of ECV at 36 weeks gestation, the proportion of breech presentation at term after BVA-T was 32%; that after EM 53%. The corresponding figures for the analysis in which ECV was performed were 12% and 19%. Without the option of ECV, the proportion of caesarean sections after BVA-T was 37%; that after EM 50%. The corresponding figures for the analysis in which ECV was performed were 23% and 28%, respectively. To prevent one caesarean section, seven women with a foetus in breech presentation at 33 weeks gestation would need to be treated with BVA-T.

Substantial differences in costs were observed between vaginal births and caesarean births.

In both analyses, the mean direct costs for BVA-T were somewhat lower than those for EM. The difference mainly resulted from the lower proportion of caesarean births associated with the BVA-T-strategy.

**Table 3.** Simulated outcomes (mean of 10,000 subjects) of BVA-T and expectant management strategies for women at 33 weeks gestation with a foetus in breech presentation.

Percentage breech presentation at delivery			
Analysis- No ECV performed	Mean (%)	OR (95% CI)	Probability SC preferred
Moxa	32.0	0.61 (0.43, 0.83)	0.0008
Standard Care	52.9		
Analysis- ECV performed			
Moxa	11.6	0.62 (0.45, 0.84)	0.001
Standard Care	18.8		

Percentage caesarean section				
Analysis- No ECV performed	Mean (%)	OR (95% CI)	Probability SC preferred	Number to treat to prevent one Caesarean
Moxa	36.6	0.73 (0.59, 0.88)	0.0008	7.3
Standard Care	50.3			
Analysis- ECV performed				
Moxa	23.1	0.83 (0.67, 0.98)	0.001	21.0
Standard Care	27.8			

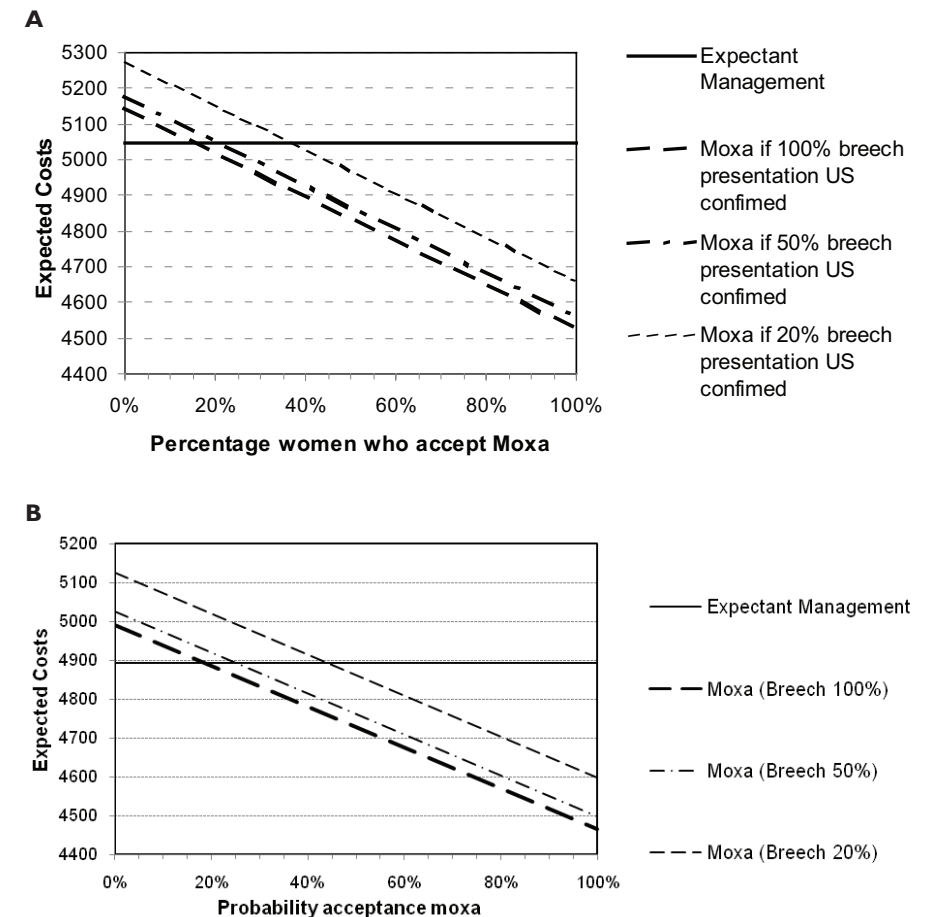
  

Total costs (2006 Euros)			
Analysis- No ECV performed	Mean (€)	Cost Difference (95% CI)	Probability SC preferred
Moxa	4595	451 (109,775)	0.0052
Standard Care	5046		
Analysis- ECV performed			
Moxa	4523	404 (72,864)	0.0073
Standard Care	4927		

Moxa = Breech version by Acumoxa  
 SC = Standard Care  
 ECV = External Cephalic Version  
 CS = Caesarean Section

### Sensitivity analysis

Sensitivity analyses were performed to evaluate the effect of the probability of a planned home birth and by varying the input parameters over the acceptance rate of BVA-T. Sensitivity analyses, in which 33.3% of all hospital



**Figure 3 (a and b)** Two-way sensitivity analysis in which the percentage of women who accept BVA-T and the percentage of breech presentations that were confirmed by ultrasound (US) were varied. The different discontinuous lines show the impact of these variables on the total costs of BVA-T. There is no influence of change in these variables on the total costs of expectant management. (a) Shows the strategies without ECV. The intersections of BVA-T with expectant management are at 16.0, 21.4 and 37.7%. (b) The strategies with ECV. The intersections of BVA-T with expectant management are at 17.6, 23.6 and 41.5%.

births were altered to home-births and care given by the midwife, demonstrated similar percentages of breech presentations compared to the main analyses and a decrease in the percentages of caesarean sections and a decrease in total costs (both with and without ECV). The percentage caesarean section was 35% after BVA-T versus 49% after EM without the option

of ECV (OR 0.71, 95% CI 0.56, 0.88); whereas this was 20% versus 25% respectively, if ECV was performed (OR 0.80, 95% CI, 0.64, 0.97).

The mean direct costs were € 4369 after BVA-T versus € 4890 after EM without ECV (cost difference € 520; 95% CI, € 135, € 883); whereas this was € 4230 versus € 4658, if ECV was performed (cost difference € 428, 95% CI € 79, € 941).

The results of sensitivity analyses performed on the percentage US-confirmed breech presentations at 33 weeks and the acceptance rate of BVA-T on the expected total costs are demonstrated in Fig. 3a and b, for the strategies without and with ECV respectively. If 100% of breech presentations are US-confirmed and the BVA-T compliance rate is 16.0% or more without ECV, or 17.6% or more with ECV, BVA-T was less costly than EM. If 20% of breech presentations are US-confirmed, the BVA-T strategy was less costly compared with EM at a BVA-T compliance rate of 37.7% and 41.5% for the strategy without and with ECV, respectively.

### Probabilistic sensitivity analysis and value of information analysis

In all scenarios and for all outcomes the probability that EM was preferred (i.e. the probability that BVA-T would not be favourable compared to EM) was less than 1% (Table 3). Assuming BVA-T was implemented instead of EM, the EVPI without and with ECV was € 0.32 and € 0.37 per woman, respectively.

## DISCUSSION

This modelling exercise aimed at evaluating the effectiveness and costs of BVA-T compared with EM for women with a foetus in breech position at 33 weeks gestation. Our analyses are consistent with a significant decrease in breech presentation after treatment with BVA-T, both with and without the option of ECV, when compared with EM. Consequently, BVA-T is associated with significantly fewer caesarean sections and therefore notably decreases the third-party payer costs. Although additional costs were attributed to BVA-T, its effectiveness corresponded with lower total costs. The results were robust in sensitivity analyses in which we varied the percentage of

breech presentations confirmed by US and the BVA-T compliance rate, and considered the Dutch situation in which 33% of births take place at home. In the Netherlands, midwifery-led care is only permitted when the foetus is in cephalic presentation. Our analysis showed that with BVA-T, without ECV, there is a 21% decrease in foetuses in breech presentation at term. These mothers with foetuses in cephalic presentation at 36-week gestation stay with or may return to midwifery-led care. Some authors showed that midwifery-led care does not lead to higher maternal or neonatal risk associated with planned home birth<sup>52,53</sup>. In addition, the value of information analysis showed that, compared to implementing BVA-T based on the currently available evidence, perfect information on the probabilities in the model obtained from further effectiveness and cost research would result in a minimal gain in expected benefit. We showed in our model with 10,000 second-order Monte Carlo simulations, that if BVA-T was implemented instead of EM, with the currently available evidence, the low EVPI makes further research of the cost effect of implementing BVA-T unnecessary. Nevertheless, we do recommend performing a well-designed RCT in a Western setting, with special attention to the safety of the Moxa technique, in line with an ongoing study in Spain<sup>54</sup>. To our knowledge, no other study has evaluated both the effectiveness and costs of BVA-T compared with EM. The results of this study, however, could guide informed decision making on the implementation of BVA-T for women with a diagnosed foetus in breech presentation after 33 weeks of gestation.

Some limitations of our study and the intervention itself should be mentioned. For one, the effectiveness data in the model had been retrieved from a meta-analysis of six RCTs in which we demonstrated positive effects of acupuncture-type interventions on BL 67, where moxibustion was used in four of the six RCT's<sup>30</sup>. Since heterogeneity was found between these studies, the random-effects model of DerSimonian and Laird<sup>55</sup> was used to pool the outcomes, thereby allowing heterogeneity in the true treatment effects. The random-effects model takes into account the variability across the studies and results in wider confidence intervals than does the fixed-effects model, which ignores the between-study heterogeneity. Part of the heterogeneity might perhaps be explained by specific study characteristics such as patients' mean age or ethnicity. In a meta-regression the study characteristics are put as covariates in a regression analysis with the estimated treatment effect of the study as dependent variable. Ideally, these covariates

should be specified in advance to reduce the risk of post hoc conclusions prompted by inspecting the available data<sup>56</sup>.

Especially when the number of studies is small, any covariate of which the value differs between the studies will be significantly related to the heterogeneity among the studies, and hence is a potential explanation of it. It is clear, however, that most of such 'explanations' will be entirely spurious<sup>57</sup>. In this regard, Lee concluded that none of the results of our meta-analysis of the six RCTs, according to ethnicity or the type of intervention, avoided heterogeneity<sup>58</sup>. However, as pointed out above, almost every study characteristic would be related to the heterogeneity between the studies and could therefore easily be based on spurious relationships. Also because the covariates proposed by Lee were not specified in advance, we think his conclusion should be interpreted with caution. However, we agree with Lee<sup>58</sup> that it would be interesting to explore the heterogeneity across studies as soon as a sufficient number of studies is available for a meta-regression. Furthermore, Vas et al. published a systematic review, which included Chinese studies<sup>59</sup>. In their analyses they evaluated in the pooled result two different treatments in the control group: expectant management and knee-to-chest-posture versus the combined effects of moxibustion with or without another technique. These results should be viewed with caution, and therefore, in this modelling exercise, we still stand for the use of the parameter-distribution of van den Berg et al, where the controls were treated with expectant management.

A second limitation of our analysis is that the follow up period was limited to 8 days postpartum and our study focused on the direct results of BVA-T on delivery mode. Therefore, indirect costs as well as effects and costs of subsequent pregnancies were not taken into account. Their inclusion, however, might well have given greater weight to the argument made<sup>60-63</sup>. Third, costs of BVA-T may have been overestimated in our analysis, as these costs included two visits to a licensed acupuncturist and two confirmative US examinations. Costs could be reduced through the use of low-cost "self-explanatory home Moxa kits" which can be ordered through the Internet. However, as breech position may be associated with congenital malformations, placenta praevia, and malformations of the uterus, we recommend that pregnant women undergo an US before she and her foetus are exposed to Moxa<sup>64,65</sup>.

Finally, the working mechanism of moxibustion is not completely known. A systematic Cochrane review concludes that there is no consensus in the literature with respect to the best regimen<sup>27</sup> suggesting that the working mechanism remains unknown. The effect of moxibustion on version might be due to the odour, the temperature, or even the specific acupuncture location<sup>28,66-69</sup>. From the acupunctural point of view, BL 67 stimulates the activity of the foetus, which may be an important mechanism to induce spontaneous version. Moreover, it seems likely that the technique may be more successful in complete breech presentations than in frank or footling breech<sup>15,21,70</sup> suggesting that the foetus itself plays a role in inducing version. Further research on the specific working mechanism and side-effects of Moxa is therefore needed.

Thought provoking is the possible beneficial effect of BVA-T in low-income countries and in rural areas far removed from medical centres. Women in these settings are less likely to undergo ECV or a caesarean section for breech presentation. The non-invasive and non-pharmaceutical BVA-T could therefore reduce infant and maternal morbidity, mortality, and medical costs in countries where poverty is an obstacle to obtaining medical care<sup>75</sup>.

## CONCLUSIONS

The results of this decision analysis suggested that for the rectification of a foetus in breech presentation in women at 33 weeks gestation, BVA-T reduced the number of breech presentations at term, the number of caesarean sections, and was less costly when compared to expectant management, including ECV.

## CONFLICT OF INTEREST STATEMENT

No competing financial interests exist. This work was partly supported by the Dutch Association for Acupuncture (N.V.A.). All authors and researchers involved state to be independent from the funding organization (NVA).

The authors' work was independent of the funding organization. The funding organization had no involvement in the study design, data collection and analysis, writing of the manuscript, or in the decision to submit this article for publication.

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Chapter **8**

**Summary, General discussion  
and Epilogue**

## SUMMARY

To provide more evidence-based results of traditional Chinese Medicine (TCM) applied to Western medicine, we studied TCM in integrated health-care. The studies in this thesis represent a range of scientific approaches to elucidate possible beneficial effects of acupuncture and moxibustion, as rooted in traditional Chinese medicine. Three fields of TCM were studied in different epidemiological ways.

First, Health related quality of life (HRQoL) was studied in a general practice for acupuncture. Although the number of patients using acupuncture in Western countries is growing, particularly among women, and musculoskeletal complaints are common in acupuncture practice, little is known about the quality of life of these patients. In the first part of this thesis, we studied the quality of life in a cohort of patients seeking treatment for musculoskeletal complaints at a general practice for acupuncture.

Second, we investigated a chronic, complex, painful and inflammatory disease, Complex regional pain syndrome (CRPS I). The chronicity of this disease combined with its complexity suggests that a holistic and personalized approach could be beneficial. More and more patients with CRPS, who do not respond well to any experimental pharmaceutical treatment regimen, turn to complementary methods that may relieve the pain, activate the diminished nutritive blood flow and help them to overcome movement anxiety and disuse or even emotional amputation of the affected limb.

Third, we considered breech presentation, for which an acupuncture-like treatment can be performed without needles and using a single prescribed point. Interestingly, the treatment can be provided by the woman's partner, so that no therapeutic relationship with the TCM practitioner is needed. In breech presentation the baby enters the birth canal with the buttocks or feet first as opposed to the normal head-first position. In many countries, caesarean section is the most common way to deliver a breech baby but, like any major surgery, caesarean section involves risks for mother and child, and for subsequent pregnancies.

To start with, **chapter 2** presents an observational study on the effect of acupuncture on health-related quality of life in patients with musculoskeletal complaints. Quality of life was reported by the patients themselves in a validated questionnaire. For the group as a whole quality of life clearly improved over the

course of treatment. Pre-treatment values on three domains – notably reflecting symptomatology – were lower than values for the Dutch population, but the post-treatment scores on these domains were even higher than the population values. The observed improvements suggest a subjective, clinically relevant, benefit of acupuncture therapy in treating musculoskeletal complaints.

**Chapter 3**, is a review of the literature on the attributive effect of acupuncture in inflammatory diseases. At the time of the study, 2003, a number of observations on the anti-inflammatory actions of acupuncture had been published, representing open studies and randomized trials. In asthma, acupuncture was most effective after an initial quick succession of treatments. In rhinitis, results that were mainly obtained from open trials suggest a complementary effect of acupuncture after allergen provocation. In inflammatory bowel disease and rheumatoid arthritis, the usefulness of acupuncture still had to be demonstrated in large randomized trials. In epicondylitis and complex regional pain syndrome type I (CRPS I), the immunosuppressive effect of acupuncture had not yet been properly investigated, and was only described in the classical Chinese textbooks. In these conditions, however, acupuncture had resulted in pain relief. As a possible mechanism underlying the observed effect we proposed that acupuncture releases the vasodilator neuropeptide CGRP from nerve endings. In this respect, acupuncture as a maintenance treatment could be beneficial to reduce inflammation.

**Chapter 4** presents a case-control study investigating whether a specified menstrual condition described in TCM as related to CRPS I, could be associated with the risk of developing CRPS I. Women suffering from CRPS I and a random selection of other women completed in this pilot study a questionnaire on menstrual cycle symptoms. Statistical analysis of the answers revealed that the women with CRPS I were over five times more likely to have had specified menstrual disorders than the controls. The results suggest that specific menstrual disorders are associated with the development of CRPS I. The TCM questionnaire used in this study could contribute to the early recognition and diagnosis of female CRPS I patients.

The third part, chapters 5, 6, and 7, is about nonvertex presentation during pregnancy and birth and additional therapies offered by a TCM practitioner during pregnancy to induce 'spontaneous' version of the nonvertex fetus.

In **chapter 5** we described the natural history of singleton breech presentation in a large cohort study and determined the prognostic value of ultrasound performed at 20 and 30 weeks of gestation in predicting nonvertex delivery. Ultrasound-confirmed nonvertex position around 30 weeks of gestation was highly predictive of nonvertex presentation at delivery, especially in nulliparous women and preterm deliveries. Ultimately, the presence of an ultrasound-confirmed breech position of the fetus around 30 weeks of gestation could be used as an indication to closely follow the fetal position and consider the use of version strategies, provided these can be performed safely and effectively, to avoid nonvertex presentation at birth.

**Chapter 6** is a systematic review including a meta-analysis of the literature. We sought to shed light on the question whether moxibustion, acupuncture, or electro-acupuncture stimulating a specific point on the small toe could correct breech presentation of the fetus with a sustained effect until delivery. On the basis of pooled results from six randomized controlled trials and three cohort studies we conclude that these acupuncture-type interventions resulted in more corrected breech presentations than wait-and-see management and a reduced number of caesarian sections. The results held for the subset of randomized controlled trials as well as for all studies combined. In a 'letter to the editor' we pointed out some differences in our study with a comparable review from another group (Addendum chapter 6).

Finally, in **chapter 7** we evaluated the cost-effectiveness of breech version by the above-mentioned acupuncture-type intervention for pregnant women with a breech fetus at 33 weeks of gestation. We did so by applying a modeling approach that compared this strategy with standard care in the Netherlands, with or without an external cephalic version at 36 weeks of gestation. At 36 weeks of gestation, when the fetus is still in nonvertex position, external cephalic version is offered. Since one third of women in the Netherlands prefer a planned home birth, we performed sensitivity analyses to account for the consequences of a fetal breech presentation during planned home births. Outcome measurements were the delivery mode and the costs. Indeed, the modeling approach showed that acupuncture-type interventions are both less costly and more effective than expectant management with or without external cephalic version.

## GENERAL DISCUSSION

In this thesis, we focused mainly on when, why and how to implement Traditional Chinese Medicine (TCM) into a healthcare concept in the Netherlands. We tried to demonstrate the value of Traditional Chinese Medicine in an epidemiological way, with evidence-based results as acceptable 'stepping stones', acquired communication tools to bridge TCM and traditional western medicine.

Indeed, it was possible to conduct and report scientifically sound studies in the area of complementary medicine in the Netherlands. It appeared that many Dutch citizens have already found their way to the general acupuncture clinic for treatment of their musculoskeletal problems, and have learned that acupuncture improves their health-related quality of life.

The diseases researched in this thesis, CRPS I and breech presentation, are mostly women's health problems. As demonstrated by the results, our main conclusion is that in these areas acupuncture, when added to standard care, is more effective and, as shown in breech version acumoxa, less costly than standard care alone. These encouraging outcomes still stand when effectiveness- and cost arguments play a role at the social level.

Although evidence-based medicine is becoming the "gold standard" for clinical practice, it carries limitations. As a major limitation, evidence-based medicine applies to larger populations, with the risk of losing sight of the individual patient. As Tonelli has said: "The knowledge gained from clinical research does not directly answer the primary clinical question of what is best for the patient at hand" and he suggests that evidence-based medicine "should not discount the value of clinical experience" <sup>1</sup>. However, the aim of medical decision-making is to perform a complete formal assessment of every aspect that is relevant to the decision. Clinicians should be proactive in decision making, and consider the problem from multiple perspectives. This includes taking patients' preferences and rare events into consideration, modeling the decision problem, and explicitly integrating risks, benefits, costs and values. This all will help both patients and doctors cope with uncertainty and fear. Milt Weinstein, an expert in the area of medical decision making, once said "The decision will be made, if not actively then by default" <sup>2</sup>.

One other obstacle to overcome before applying an additional ‘new’ therapy, and one of the stepping stones to cross over should be the credo “First do no harm” (Hippocrates oath).

The reviews and results of the study about the prognostic value of ultrasound on the natural pathway of the presentation of the fetus are of importance to both the clinician and the TCM practitioner. Having knowledge of this basic information is imperative before one can decide on the best possible therapy for each individual patient.

There is no doubt that acupuncture research is beginning to be taken seriously. Peer reviewed literature shows the strength and limitations of Traditional described Chinese Medicine in many clinical and epidemiological disciplines. In the Netherlands, the academic infrastructure into TCM research is fragile, but developing. However, this thesis is only the first stepping stone of the Dutch crossover between TCM and conventional western medicine, although the main conclusion of this thesis may seem clear and unambiguous.

Yet, there are different ways of looking at TCM. Therefore, in this final chapter, we will present the perspectives of, respectively, the patient and her family, the general practitioner, the TCM practitioner, the health insurers, and the policymakers and health economics researchers.

After presenting these five different perspectives, we will elucidate how science could provide deeper understanding of the possibilities of acupuncture in complementary healthcare and, in additionally, the role of science in the world of complementary medicine practitioners.

### **PERSPECTIVE I: The patient and her family**

The results that will most likely catch the eye of the patient and her family include characteristics attributable to their health perspective compared to that of the Dutch population. When confronted with a (chronic) disease, people may go in search for other ways to manage their main complaint: pain. Patients may have found information about acupuncture practices via all kinds of new and old media, or have been told about acupuncture by others. However, although more and more patients in western countries turn to acupuncture,<sup>3-5</sup> and musculoskeletal complaints are common in acupuncture practice<sup>6,7</sup>, little is known about the outcome of using acupuncture treatments.

In the Netherlands, acupuncture treatments can be entered into without a referral from the GP. In the study presented in this thesis (chapter 2), most patients found their way to the TCM practitioner themselves, and completed the acupuncture treatment, even if they had to (partly) pay themselves. Licensed professional acupuncturists in the Netherlands stand for accurate information about acupuncture. Therefore the (naïve<sup>1</sup>) study patients were informed about the likely benefits and risks of acupuncture, and the acupuncturist obtained an informed consent before commencing with the treatments.

Interestingly, at the beginning of the treatments the quality-of-life scores of the naïve study patients were significantly lower compared to the Dutch population sample pertaining to the three physical domains: role-physical limitations, bodily pain and social functioning, in contrast to mental health summary scores. During the course of treatment, the scores increased significantly for five domains: physical functioning, role-physical functioning, bodily pain, social functioning and vitality. Notable improvements in the last two qualities were observed by the patients’ relatives, who then were or may in the future be more inclined to turn to an acupuncturist as well when developing musculoskeletal complaints themselves.

The occurrence of CRPS I after trauma or surgery is still not completely understood. The continuing pain, abnormal limb temperature, edema and dysfunction have great impact on the patients’ daily functioning and quality of life. De Mos and colleagues<sup>8</sup> provided an overview of the current understandings on the pathogenic mechanisms that underlie CRPS I. Western diagnostics often involve a spate of laboratory tests and measurements, which might be a reason for possible late recognition and treatment of CRPS I.

Chinese diagnostic methods stress the practitioners’ perceptions, judgment, intuition and experience. The TCM practitioner takes stock of what she sees, hears, smells and feels. She will also lend a willing ear to the patient’s feelings and (other) complaints, and enquire about daily activities. The patient and the TCM practitioner work together to define the patient’s present condition and to find reasons for any aberrations. Just as in any cell of the body the DNA is stored as a template of the entire organism, Chinese philosophy states that any part of the body (pulse, tongue, ear, men-

1 naïve means no previous experience of acupuncture treatments

strual cycle) reflects information about the whole. This diagnostic thinking is reflected and researched in chapter 4.

In my clinical work, I inform the women with CRPS I about the TCM diagnosis, and discuss the possible cause of their disease. Often they recognize the pattern of imbalance and accept this as a reliable explanation for the delayed recovery of the trauma that somehow initiated CRPS I. They are then more motivated to work on improvement using exercise and diet.

Also in the area of preventive medicine, patients find or are offered TCM treatments. In the Netherlands, when a breech diagnosis is made, there is a more than 80% chance of a cesarean section<sup>9</sup>. The pregnant woman or both parents may take the view that it would be preferable to avoid this major surgery and start searching for more information. Currently there are more than 26,000 websites pointing them to potential operation-sparing Moxa-treatment by the acupuncturist! In the decision analysis (chapter 7), we demonstrated that in the total sample, where breech presentation is confirmed by ultrasound at 33 weeks, only seven women would need to be treated with breech version by acupuncture-type interventions on BL 67 to avoid a cesarean section.

After the intake consultation with the acupuncturist, the parents may want to discuss with their GP issues arising from this private consultation and ask him/her to arrange the referral. Patients appreciate reliable information from their GPs and specialists on TCM as well<sup>10</sup>, and almost 75% of the Dutch population feels the need to consult the GP about complementary medicine<sup>11</sup>. Two thirds of the Dutch population wants their GP to be in favor of the treatment and 98% would like to see their GP keeping pace with the treatment results<sup>12</sup>. However, it is the patient's obligation to explore the new perspectives and suggestions offered by their doctor.

## **PERSPECTIVE 2: The general practitioner and the midwife**

The populations studied in this thesis can be found in the waiting rooms of a GP or a pain-specialist (musculoskeletal problems and CRPS I) or a GP, midwife or gynecologist (breech presentation). Traditionally, the clinician used to be the sole decision maker in healthcare, but nowadays, two-way communication is the basis of good healthcare. A GP or midwife will support the parents in coming to terms with the new situation and share with them how others have managed in similar circumstances. The GP or midwife cannot be expected to have all the answers, but they will help to find them. Overall, GPs are of the opinion that it is their task to provide their patients with (evidence-based) information about (additive) complementary and alternative medicine (CAM) treatment possibilities; 75% think they must be knowledgeable about the most applied CAM treatments and that their patients should communicate with them about CAM<sup>13</sup>.

The majority of the GPs have focused on studying conventional western medicine. Therefore the notion that a pinprick - often in a part of the body far removed from the affected area - can cure an illness, is alien to them. Even when told by patients about their recovery after acupuncture, GPs will find this hard to believe without evidence-based and published results. Some doctors or patients may even wonder how one can practice such a form of medicine.

However, just as a doctor will prescribe paracetamol because she knows its effect on the patient's body, an acupuncturist will needle a certain point because of the known consistent reactions of the diseased human body. And yet both, the doctor and the acupuncturist, may have only a limited understanding of the pathway of the bodily effects of their respective treatments. Nevertheless, our observational study on the effect of acupuncture on health-related quality of life in patients with musculoskeletal complaints lends itself to giving the GP an insight in TCM in a general acupuncture practice.

The second part of the thesis deals with making diagnoses. To make a correct diagnosis, a GP has to explore all the possible reasons for the symptoms, which may take some time. GPs may fail to clearly diagnose CRPS I, even after specialist tests and advice. The pathophysiology of CRPS I is poorly understood. Worldwide there seems to be a gender disposition toward CRPS I: 75% of patients are women, with a median age of 46 years.

Menstrual cycle-related problems in the year before CRPS I developed have been described, but an association between the development of CRPS I and cumulative endogenous estrogen exposure has not been found<sup>8</sup>.

In chapter 4, we investigated whether the risk of developing CRPS I is associated with the TCM painful obstructive syndrome (POS). In TCM, menstrual disorders are related to the state of women's constitution and therefore menstrual disorders identify their pain patterns. We selected, translated and administered a special questionnaire on disorders of the menstrual cycle to find an additional way to diagnose CRPS I. The results suggest that selected menstrual conditions are associated with the risk of developing CRPS I. Based on this knowledge the GP may be recommended to include a menstrual cycle history in the evaluation of her female chronic CRPS I patients. While the TCM questionnaire about menstrual symptoms and signs could contribute to the early recognition and diagnosis of complex pain problems in women, the derived questionnaire related to POS could help diagnose CRPS I.

The third part of this thesis concerns breech presentation. The results (chapters 5 and 6) could help both the GP and midwife to make an informed decision on the implementation of Moxa for women with a diagnosed fetus in breech presentation after 33 weeks of gestation. Watson and colleagues, showing that the accuracy of assessment of breech presentation depends on the individual obstetric care provider, reported that 57.1% of the breech presentations were identified correctly<sup>14</sup>.

When breech presentation is confirmed by ultrasound at 30 weeks and when no (relative) contra-indications for acupuncture-type interventions are present, Moxa treatment can be started at 33 weeks gestational age. The period in-between seems the right time window for the GP, gynecologist and midwife to discuss the mother's and her fetus's condition and the possibility of TCM treatment with the TCM practitioner. In clinical decision making, patients and doctors assumingly speak the same language, but their focus will differ. The GP and midwife have to weigh the health state of both the mother and her fetus, as well as psychosocial issues. It is the GP's responsibility to interpret the patient's progress and to guide her and / or her partner in collaboration with the TCM practitioner. She should be aware of current trends in CAM, including possible interactions with other medication<sup>15</sup>.

### **PERSPECTIVE 3: The TCM practitioner**

There are no legal restrictions to practice TCM in the Netherlands. "Full service" Chinese medical practitioners can provide Chinese herbal therapy, Chinese (eastern) nutritional counseling and Asian body work, in addition to acupuncture. Licensed acupuncturists are differently trained than medical acupuncturists in providing acupuncture services. A western medical diagnosis can only be made by a medical doctor. Even training among licensed acupuncturists can vary widely. Some graduate programs include training in all aspects of Chinese Medicine, including Chinese herbal therapy, food therapy and body work.

The TCM approach is interesting in that it offers simultaneous therapies for the treatment of pain and many other concurrent somatic (e.g. edema) and psychological disturbances (e.g. insomnia). The acupuncturist's most important skill is to know which acupuncture point is used to pierce the skin in relation to which disease. With her knowledge, the acupuncturist can differentiate and personalize what in western medicine is collectively described under one name. Compare the many words in the Inuit language describing the great varieties of snow.

However, one of the pitfalls that the TCM practitioner has to guard against is a tendency to act as a GP. As seen in chapter 2, the typical out-patient is not referred by the GP and the main complaint is physical dysfunction. In the consultation process of attentive listening to and observing the patient, and helping them with the lifting and untangling of the habitual and stagnating flow of Qi – or tangled ideas – the TCM practitioner should be aware of 'red flags' in the patient's medical history, similar to recognizing 'red flags' in physiotherapy. Any 'red flags' should alert to possible boundaries of the treatment, upon which the GP must be consulted. TCM indeed has always been concerned with guaranteeing safety for the patient. However, a good contact with the GP and other caregivers is in the interest of all concerned; therefore the patient should always be asked to consent to providing their GP with details of the consultation. Of course it is the patient's right to refuse such consent.

A special area for TCM is maternity care and obstetrics. Some general conditions that in modern medicine are treated with drugs that may harm the unborn baby had better be treated by acupuncture in order to avoid the risk of harmful side-effects. Acupuncture has shown effective in treating certain



problems that may occur during pregnancy<sup>16</sup>, such as extreme morning sickness<sup>17 18 19</sup>, malposition of the fetus<sup>20</sup>, or depression during pregnancy<sup>21</sup>. Traditionally, specific treatments are also given to the mother during the pregnancy to aid the fetus's development.

Although the practice as described in chapters 5 and 6 is familiar to every acupuncturist, some issues need to be addressed. When a woman with a fetus in breech presentation comes to the clinic, her overall state of health is also taken into account in the personalized needle prescription. Extra needles may be added to Bl 67 to cover additional problems of mother and child. However, even then, in all cases intervention is kept to a minimum. Additionally, any personal preferences should be taken into account and the practitioner would do well to mention the smell and warmth involved in the moxibustion treatment. Continuing education in obstetrics should be recommended for TCM practitioners working in obstetrics.

#### **PERSPECTIVE 4: The Health Insurers**

The most important goal of a health insurance company is to offer a wide variety of programs and services that can help improve health and well-being of their clients while saving and planning for future costs. One way to do so is to add complementary medicine therapies to the personal indemnity insurance. The most researched therapy is acupuncture. Being safe and cheap in itself, it can even prevent interventions such as cesarean sections, and thus also save money, as described in chapter 7.

Furthermore, apart from its given equal or more positive results, acupuncture treatment usually spans a longer period – and may therefore contribute to 'natural' recovery as a result of the body's self-healing capacity. If this should happen, the more expensive (diagnostic) interventions may be superfluous. However, this positive aspect would be more convincing if the health insurers can be encouraged to take more initiatives to conduct related research.

Evidence-based medicine aims to address the persistent problem of clinical practice variation with the help of various tools. The mixed record of evidence-based medicine are rooted in the traditional perspective of the clinician as sole decision maker<sup>22</sup>. Multifaceted implementation strategies

that take the collaborative nature of medical work into consideration promise more effective changes in clinical practice, as evidenced by the popularity of complementary and alternative medical therapies. The main issue of the current credentialing debate is the question: "Who resolves which providers and therapies will be accepted as safe, effective, appropriate, and reimbursable?" Please note, right now, this debate is especially vital in the patient associations, who urge the health insurance companies to initiate more research.

In the Netherlands, personal indemnity insurance for practitioners covers acupuncture. That is, under the pressure of several powerful patient associations, the health insurance companies in the Netherlands have been found willing to (partly) reimburse acupuncture treatment, as it is shown to be a relative safe intervention<sup>23, 24</sup>. Most insurance companies refund acupuncture (not herbs) costs up to a set maximum if the practitioner is a member of one of the three professional organizations. (NVA, NAAV and NVTC, see appendix I: glossary)

#### **PERSPECTIVE 5: The policymaker and the health (economics) researcher.**

In the Netherlands there is no governmental involvement whatsoever in courses for acupuncture. In the USA, Canada, France and Germany, however, state legislatures and professional medical organizations have developed mechanisms to license physicians and other conventional non-physician providers of CAM<sup>25</sup>.

Healthcare policy makers, researchers, and providers continually receive large amounts of information from patient organizations, TCM practitioners and doctors. They still wonder, however, whether this information actually provides the right answers about the different effect outcomes of TCM. People who resort to acupuncture and Chinese medicine for long-term health problems have been found to experience a range of different effects and results<sup>26</sup>. A precondition for studying the effectiveness of TCM is to develop outcome measures that include as many of these diverse effects as possible. Similar problems face researchers investigating other types of complementary therapies and the even more complex interventions of integrative care. Verhoef and colleagues have developed outcome measures for integrative care<sup>27</sup> and suggested that a combination of objective measures, self-report questionnaires and qualitative methods is required<sup>28</sup>.

Pragmatic studies like HRQoL and cost-effectiveness studies are important to show patients' willingness and compliance to accept and undergo the TCM therapy. Alas, such studies are rare. In western countries, musculoskeletal complaints are an important cause of disability, morbidity<sup>29</sup>, absence from work<sup>30</sup> and increased healthcare costs<sup>31, 32</sup>. In a large population-based study in the Netherlands, 75% reported having had musculoskeletal complaints during the past year, and 44% reported chronic musculoskeletal pain<sup>33</sup>. About half of those contacted a health professional for their symptoms, thus drawing considerably on healthcare services. Denying the real practice, this study did not take into account those who turned to CAM practitioners such as acupuncturists.

It is clear that the health economics researcher needs the systematic review to efficiently integrate existing information and provide data for rational decision making. Systematic reviews notice whether scientific findings are consistent and can be generalized across populations, settings, and treatment variations, or whether findings vary significantly by particular subsets. Indeed, our meta-analyses in particular can increase power and precision of estimates of breech-version-acupuncture-type-treatment (BVA-T) and breech presentation at delivery, while limiting possible bias.

The results described in chapters 5 should also help policy makers to make informed decisions regarding the implementation of an additional ultrasound study in pregnant women at 33 weeks. Informed birthing decisions cannot be made without information on success rates of all strategies, and any necessary tradeoffs between the two<sup>34, 35</sup>. We showed that implementation of Moxa for women with a diagnosed fetus in breech presentation after 33 weeks of gestation could contribute to a lower number of breech newborns. Additionally, even when the effectiveness of the TCM treatment equals standard care, the health (economics) researcher should pay more attention to the benefits of TCM treatment: avoiding the risks of medical drugs, the relatively small side-effects and the relative cost-effectiveness of the TCM treatment compared to standard treatment<sup>23</sup>.

In chapter 7 we performed a value of information analysis (VOI). This analysis was introduced to estimate the expected benefit of a further study. Thus, VOI analysis evaluates uncertainty resulting in a formal comparison of the expected benefit and the cost of a proposed study. Interestingly, in using this justified method to study a 3,000 year old intervention as moxibustion, which likely will still work 3,000 years from now, we met a difficulty to apply

within the formula. In the formula, the years that the intervention is possibly working in this area is in the divider! Consequently, additional information about new studies about moxibustion seems to be always low.

Furthermore, the VOI showed that if one assumes that breech version acumoxa treatment was implemented in the care for women with a fetus in breech at 33 weeks of gestation (instead of waiting and observing), the expected value of perfect information, (the result of a real RCT as now modeled), without and with external cephalic version, was only € 0.32 and € 0.37 per woman.

All in all, there is a role for the health economics researcher in the field of additional research. New pragmatic studies of the currently-used TCM therapies, as well as better understanding of behavioral traits of chronic (pain) patients in their search for relief, care and support may bring to light the limited ability to adequately control the use of TCM. On the other hand, policymakers now advocate the implementation of evidence based techniques in healthcare.

The following questions still need to be answered:

- Do the Dutch embrace complementary healthcare? If so, what are the consequences? Are there any dangers? Or does it contribute to good health in our society?
- What roles do the complementary medicine practitioners in the Netherlands envisage? What do they find important? Where are their loyalties? Are there any data on these aspects?
- What already moves millions of people in the western world to use Chinese medicine as a cure for bodily complaints? Why is it that this curative system, including acupuncture, moxibustion, qi gong and herbal medicine, fits so well in the modern wellbeing and health concept?

## EPILOGUE

Hopefully this thesis invites the reader towards a collaborative understanding that will allow TCM to be applied to modern diseases and to be evaluated by evidence-based methods of clinical research. As Ted Kaptchuk said: "Acupuncturists require flexibility, the ability to treat the whole person and the recognition of the legitimacy of Chinese diagnostic categories for selecting treatment. Western researchers generally require reproducibility, standardization, and blind assessment. While each side makes some compromises, the authenticity of both sides remains undiminished. A new synthesis is created and one can even speak of a new era of responsible and honest relationship between Chinese medicine and biomedicine."<sup>36</sup>

We have seen that the Netherlands healthcare system gives room to complementary healthcare. Notably, many chronically ill already seek complementary treatment; a number of health insurers indeed (partly) covers such treatment through a supplementary health insurance plan. The world of medical science tends to frown upon this practice of complementary treatment, and it has still not decided whether it is dealing with quackery or reliable treatment methods. Here, the task of science is to scrupulously study aspects of complementary healthcare and to publish the results.

I contend, however, that the current research focuses almost exclusively on the strictly orthodox variants of complementary healthcare, for example by emphasizing a practitioner's unidirectional approach and by discouraging clients' access to Western modern medical care. There is no doubt that society should fight - and already is fighting - such practices .

But does this focus give a true picture of, for example, the role of acupuncture in complementary healthcare and the world of complementary medicine practitioners? As a TCM practitioner and an acupuncturist myself, I believe that there is still not enough room allocated in the big house of medical healthcare to the different types of complementary care.

Secondly, it strikes me that the concept of 'complementary healthcare as part of the general healthcare' is often associated with national healthcare problems such as quackery, doctors' delay and patients' delay. We should not forget that it is not the common acupuncturist or other complementary

healthcare practitioner but rather the opportunistic 'quack' who perpetrates the (negative) stereotype of complementary care in the public mind. This stereotype is repeatedly reinforced, especially when evidence of the lack of proper care is found when a 'quack' counsels terminally ill patients without consulting their doctors, and stories abound in the popular media. Then, I fear, complementary care is often wrongly associated, consciously or unconsciously, with quackery and even criminal practices, while a general lack of understanding and isolation of the individual patient looms in the background. As a result, applying integrative medicine as part of western modern care for the modern well-informed patient may come under scrutiny as well.

Finally, I suggest that scientific knowledge and modern evidence-based insights about complementary care are disregarded in general, or at least are rarely brought up, which I find deeply regrettable. Since science aims to be objective and truth-seeking, science can be the bridge to put the debate in order. This holds true at least for the Western world, with its long-standing tradition of adequate evidence-based research into the effectiveness and safety of complementary care, and its professed willingness to seriously consider implementation of complementary care.

Complementary care and complementary medicine practitioners are by no means new phenomena. Science has a great opportunity and a clear task to shape the social debate and include these phenomena into a more balanced practice of Western medicine. To this end, science should strive to bring into the limelight the whole range of views and insights encountered in the world of complementary medicine practitioners.

Currently, however, it appears that science is not actively engaged in furthering this task. A good example is the lukewarm reception of the work of top researchers such as McPherson, Langevin, Pomeranz, Paterson, Hui, Kong and Ahn<sup>37-40</sup>. Based on years of modern evidence-based research by these world-renowned experts in the field of acupuncture, their studies are true eye-openers to the many opportunities for using acupuncture and the great variety of uses available.

Especially when there is evidence suggesting that acupuncture is as effective as other active therapies, the use of acupuncture should be considered more closely, and acupuncture should receive more credit than it does presently<sup>46</sup>. In spite of thorough reviews and discussions in the peer reviewed journals, including JAMA<sup>41</sup>, Lancet<sup>42</sup>, BMJ<sup>43,44</sup> and Pain<sup>45</sup>, Western healthcare has rather neglected the experts' findings, which is one of the reasons why these conclusions have hardly reached the politicians and other policy-makers. The world of science has the opportunity to play an unbiased role in the study and dissemination of information about the use of acupuncture and moxibustion; the aim of evidence-based research is the eventual implementation of studied interventions such as acupuncture. Unfortunately, right now it appears that universities may not see their participation in the social debate as a major responsibility. However, I strongly contend that scientists do have a social task here in view of the very objectivity that characterizes their work.

### Recommendations

There is no doubt that TCM research is beginning to be taken seriously. The literature shows work in many clinical and epidemiological disciplines. In the Netherlands, the academic infrastructure of TCM research is fragile, but developing. Indeed, this thesis gives positive observations confirming that implementation of complementary healthcare and complementary medicine practices are justified in modern Western medicine.

Additionally, the areas of acupuncture I researched showed a reliable health science, with additive qualities for (chronically) ill people and for preventive care in obstetrics. Secondly, we showed that the holistic point of view, used in the specific acupuncture consultation about the menstrual cycle may be the key to acupuncture's therapeutic success in pain relief. Nevertheless, safety issues need to be addressed. Therefore, in this thesis we plea for an additional ultrasound study in pregnant women at 30 weeks, not only for its prognostic value, but also to build in a tool to select only women with a low risk pregnancy for additionally offered CAM therapies.

Patient safety is the responsibility of the therapist practicing TCM or the TCM doctor, which means a membership of a professional organization. This guarantees the professional conduct of their members and adopts rules

of ethics, privacy and patient information, including complaints and disciplinary proceedings. In addition, members are obliged to follow annual training. The high standards of hygiene, sterility and safety during the treatment are set by the professional organization.

Acupuncture research brings many professionally working acupuncturists into direct contact with traditionally trained academic colleagues from a variety of different backgrounds. I trust this will lead to more recognition, collaboration and intervision of each other's capacities. Science should embrace the fact that it is empowered to raise its voice in the social debate on the complementary-care-searching practices of the mature, modern and assertive patient.

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Chapter 9

**Nederlandstalige samenvatting**



Dit proefschrift richt zich op de toepassing van de traditionele Chinese geneeskunde binnen de westerse geneeskunde. Om meer evidence-based resultaten van de traditionele Chinese geneeskunde (TCG) te kunnen toepassen in de westerse geneeskunde, bestudeerden we de TCG geïntegreerd in de gezondheidszorg. De studies in dit proefschrift vertegenwoordigen een scala van wetenschappelijke benaderingen van mogelijke positieve effecten van acupunctuur en Moxa therapie, zoals deze verankerd zijn in de traditionele Chinese geneeskunde.

De aanpak was gericht op onderzoek naar de volgende drie medische aandachtsgebieden door middel van verschillende epidemiologische methoden, namelijk:

1. Onderzoek naar de gezondheidsgelateerde kwaliteit van leven van patiënten in een algemene praktijk voor acupunctuur.
2. Onderzoek naar Traditionele Chinese geneeswijzen bij chronische inflammatoire aandoeningen, waaronder het complex regionaal pijnsyndroom (CRPS I)
3. Onderzoek naar de effectiviteit en de kosten van een TCG behandeling om "spontane draaiing" van stuitligging gedurende de zwangerschap te bewerkstelligen.

#### ***Ad 1. Onderzoek naar de gezondheidsgelateerde kwaliteit van leven van patiënten in een algemene praktijk voor acupunctuur***

Als eerste hebben we, in een pilotstudy, de gezondheidsgelateerde kwaliteit van leven (HRQoL) bij patiënten in een particuliere praktijk voor acupunctuur bestudeerd. Steeds meer mensen in westerse landen nemen hun toevlucht tot acupunctuur. Op eigen initiatief melden patiënten met rug-, spier- en gewrichtspijnen (de zogenoemde musculo-skeletale aandoeningen) zich. Er is echter maar weinig bekend over het verschil in HRQoL tussen deze groep patiënten in vergelijking met de HRQoL van de Nederlandse populatie. Bovendien is er weinig bekend over de HRQoL van die patiënt voor en na de acupunctuurbehandeling.

Hoofdstuk 2 beschrijft daarom een observatiestudie naar het effect van acupunctuur op de gezondheidsgelateerde kwaliteit van leven bij patiënten met musculo-skeletale aandoeningen. De 26 patiënten, die nooit eerder behandeld zijn met acupunctuur, vulden voor en na de behandeling een gevalideerde vragenlijst in (RAND-36). De RAND-36 is een door de patiënt zelf in te vullen

vragenlijst naar algemene gezondheid, zowel psychisch als lichamelijk, verdeeld in 8 domeinen. Door het invullen van deze vragenlijst kan worden gemeten in hoeverre het functioneren in welk domein wordt gehinderd. De algemene conclusie luidt dat voor de groep als geheel de kwaliteit van leven duidelijk verbeterd was in de loop van de behandeling. Voorafgaand aan de behandeling waren de waarden op drie domeinen - in het bijzonder die domeinen die gerelateerd waren aan lichamelijke klachten - lager dan de waarden voor de Nederlandse bevolking. Na de acupunctuurbehandeling waren de scores op deze domeinen zelfs hoger. De na de acupunctuurbehandeling waargenomen verbeteringen suggereren een subjectief, klinisch relevante verbetering in de HRQoL, bij de behandeling van klachten aan het bewegingsapparaat.

#### ***Ad 2 Onderzoek naar Traditionele Chinese geneeswijzen bij chronische inflammatoire aandoeningen, waaronder het complex regionaal pijnsyndroom (CRPS I)***

In het eerste deel, hoofdstuk 3, wordt een overzicht van de wetenschappelijke literatuur over het toegeschreven effect van acupunctuur bij ontstekingsziekten beschreven. Op het moment van de studie, (2003), waren een aantal observaties over de ontstekingsremmende werking van acupunctuur gepubliceerd in de vorm van open en gerandomiseerde trials. Hieruit kunnen de volgende conclusies worden getrokken. Bij astma bleek acupunctuur het meest effectief als de acupunctuurbehandelingen snel toegepast werden en elkaar snel opvolgden. Bij rhinitis suggereren de uitkomsten, die hoofdzakelijk verkregen waren uit open trials, een gunstig effect van acupunctuur na blootstelling aan allergenen. Bij inflammatoire darmziekten en reumatoïde artritis moet het nut van acupunctuur nog blijken uit grote gerandomiseerde trials. Het immunosuppressieve effect van acupunctuur, zoals beschreven in de klassieke Chinese leerboeken, was voor epicondylitis en complex regionaal pijnsyndroom type I (CRPS I) nog niet goed onderzocht. Niettemin resulteerde acupunctuur bij deze aandoeningen wel in meetbare pijnverlichting.

Als een mogelijk mechanisme dat ten grondslag zou kunnen liggen aan het waargenomen effect voeren wij aan dat het vaatverwijdende neuropeptide CGRP vrijkomt onder invloed van de acupunctuurbehandeling. Wat dit betreft zou acupunctuur als onderhoudsbehandeling een gunstige invloed kunnen hebben op het verminderen van de ontsteking en daarmee de pijn.

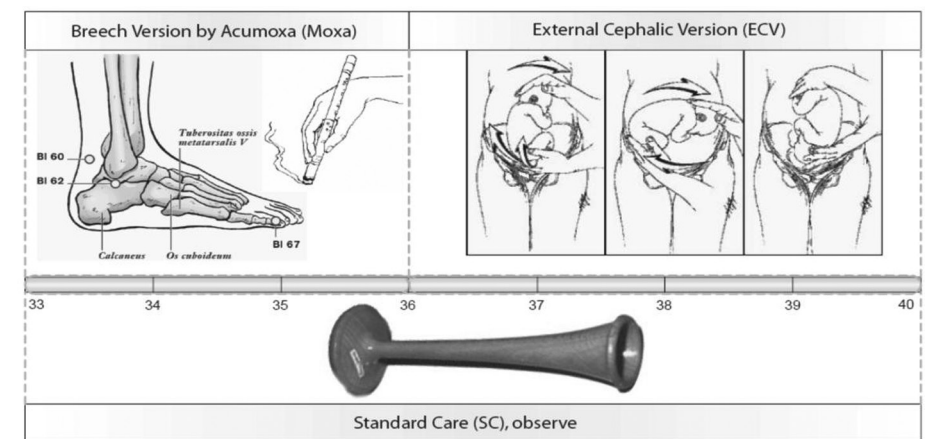
Het tweede gedeelte, hoofdstuk 4, betreft het Complex Regionaal Pijnsyndroom (CRPS I): een chronische aandoening die gepaard gaat met veel pijn,

zwellingen en temperatuurverschillen in armen of benen. Andere symptomen die kunnen optreden zijn bewegingsbeperkingen, een verandering in het zweetpatroon, verkramping van handen en voeten (dystonie) en veranderingen in huid, haargroei en nagelgroei. CRPS I stond voorheen overigens bekend onder de naam posttraumatische dystrofie (PD), Südeckse dystrofie of sympathische reflexdystrofie. Het is niet bekend waarom sommige mensen onder bepaalde omstandigheden CRPS-I ontwikkelen als complicatie van een breuk of kneuzing en andere mensen onder dezelfde omstandigheden deze invaliderende complicatie juist niet ontwikkelen. Vroege herkenning van CRPS I is echter belangrijk, omdat men in dat geval snel met de behandeling te beginnen. Hierdoor kan mogelijk worden voorkomen dat het ziektebeeld ernstiger wordt. De diagnose CRPS-I wordt overwegend gesteld op grond van de klachten en het lichamelijk onderzoek. Er zijn momenteel geen laboratoriumtesten voorhanden om de diagnose te bevestigen. Wel is bekend dat rond 75% van de CRPS I patiënten vrouw is. In dit hoofdstuk wordt een patiënt-controle onderzoek gepresenteerd waarin is onderzocht of een vooraf omschreven menstruatieverstoring - zoals beschreven in de TCG - kon worden geassocieerd met het risico op het ontwikkelen van CRPS I. De pilot-studie beschrijft een groep van 34 vrouwen die lijden aan CRPS I, en gediagnosticeerd door een anesthesist, en een controle groep van 147 willekeurig geselecteerde andere vrouwen die niet aan CRPS I lijden. Beide groepen vulden een vragenlijst in over 59 mogelijke symptomen bij een menstruatiecyclus. Uit de statistische analyse van de antwoorden hierop bleek dat de vrouwen met CRPS I 5,2 keer vaker de specifiek beschreven menstruatiestoornis hadden dan de vrouwen uit de controlegroep. De resultaten tonen aan dat de in de TCG beschreven, aan CRPS gerelateerde menstruatieverstoring is geassocieerd met de ontwikkeling van CRPS I ooit. Toepassing van de uitkomsten van deze vragenlijst, zoals die gebruikt wordt in de anamnese in de TCG praktijk, zou kunnen bijdragen aan het tijdig herkennen en diagnosticeren van vrouwelijke CRPS I patiënten.

### Ad 3. Onderzoek naar de effectiviteit en de kosten van een TCG behandeling om "spontane draaiing" van stuitligging gedurende de zwangerschap te bewerkstelligen

In het derde deel, de hoofdstukken 5, 6, en 7, worden de nonvertex presentatie (stuit- en dwars-ligging) tijdens de zwangerschap en geboorte en de effectieve, aanvullende en complementaire therapieën vanuit de TCG beschreven. Door deze TCG behandeling is het mogelijk gebleken om op deze manier iets eerder tijdens de zwangerschap de 'spontane' versie van de nonvertex foetus te initiëren, en wel voorafgaand aan periode waar de uitwendige versie (ECV) uitgevoerd wordt (Figuur 1). Daarmee kan de ECV in een aantal gevallen uiteindelijk worden voorkomen. Tijdens de zwangerschap kan de foetus met het achterwerk of stuit naar beneden liggen. Deze ligging is niet optimaal voor het baren. Keert de foetus zich niet tijdens de zwangerschap, dan is in 80% van de zwangerschappen van een eenling uiteindelijk een keizersnee nodig. Aan die ingreep zijn naast de gezondheidsrisico's voor moeder en kind, ook hoge kosten verbonden. Bovendien heeft deze operatie een nadelige invloed op verloop en gezondheidszorg bij de volgende zwangerschappen.

**Figuur 1**



In hoofdstuk 5 hebben we het natuurlijke verloop van eenlingzwangerschappen met stuitligging beschreven in een groot cohort-onderzoek: Generation R. We hebben gekeken naar het percentage stuitliggingen bij de bevalling. Daarnaast onderzochten we de voorspellende waarde van echo-

grafie bij 20 en 30 weken in de zwangerschap op de ligging bij de geboorte. Gebleken is dat stuitligging, bevestigd door echografie rond 30 weken in de zwangerschap, een hoge voorspellende waarde heeft voor de ligging tijdens de geboorte. Dit speelt vooral bij een eerste zwangerschap of een vroeggeboorte. Een stuitligging rond week 30 is een indicatie om de moeder en de positie van haar foetus goed te volgen. Daarnaast kunnen dan ook aanvullende en bewezen effectieve behandelingen worden overwogen om de stuitligging te keren (Figuur 1). Hierbij geldt wel het voorbehoud dat deze behandelingen ook veilig kunnen worden uitgevoerd.

In de Chinese en westerse wetenschappelijke literatuur worden vele onderzoeken beschreven met TCG gerelateerde behandelmethoden om de foetus in stuitligging gedurende de zwangerschap te keren. De belangwekkendste TCG behandeling is de Moxa therapie. Moxa therapie behandeling (moxeren) maakt geen gebruik van naalden, maar van een brandende Moxa-staaf. Dit is een rol aangestoken bijvoetskruid (*Artemisia Vulgaris*), die ongeveer een duimbreedte boven een acupunctuurpunt wordt gehouden. De toegediende warmte is de prikkeling van het acupunctuurpunt. De behandeling spitst zich toe op één enkel aangewezen acupunctuurpunt aan de buitenzijde van de kleine teen (ZhiYin, BL 67). Het interessante van deze behandeling is dat ze, na een introductie en instructie van de acupuncturiste, aan de partner van de zwangere vrouw kan worden geleerd. De partner kan vervolgens, in de aansluitende 14 dagen, de moxa-therapie zelf thuis geven. Dit zonder verdere tussenkomst van een beoefenaar van de traditionele Chinese geneeskunst.

Hoofdstuk 6 is een systematische review met een meta-analyse van de wetenschappelijke literatuur van de TCG-gerelateerde behandeltechnieken van acupunctuurpunt 'Blaas 67'. De vraag die beantwoord moest worden was of *moxibustion*, acupunctuur, of electro-acupunctuur waarbij een bepaald punt op de kleine teen wordt gestimuleerd, kan leiden tot kering van de stuitligging en behoud van de nieuwe positie tot de geboorte. Op basis van de gezamenlijke resultaten van zes gerandomiseerde, gecontroleerde trials en drie cohort-studies concluderen we dat deze acupunctuurtoepassingen leiden tot meer hoofdliggingen dan bij een afwachtende houding. De bijlage bij dit hoofdstuk is een 'letter to the editor' waarin we hebben gewezen op enkele verschillen in onze resultaten ten opzichte van een vergelijkbare review van een andere onderzoeksgroep.

Ten slotte wordt in hoofdstuk 7 de kosteneffectiviteit behandeld van de kering van stuitligging bij 33 weken in de zwangerschap met behulp van bovengenoemde acupunctuur-toepassingen. Met behulp van een simulatiemodel is deze behandelingsmethode vergeleken met de gebruikelijke standaardzorg in Nederland (dus met of zonder uitwendige kering bij 36 weken). In het model wordt de uitwendige kering voorgesteld in de situatie dat er nog steeds sprake is van stuitligging bij 36 weken. Aangezien een derde van de zwangere vrouwen in Nederland de voorkeur geeft aan een geplande bevalling thuis, hebben we sensitiviteitsanalyses toegepast waarin rekening werd gehouden met de gevolgen van stuitligging bij geplande bevallingen thuis. Er waren twee invalshoeken belicht: de wijze van bevallen en de kosten. Uit de berekeningen bleek dat de acupunctuur-toepassingen (i.c. de moxa-therapie) minder kostbaar zijn en effectiever, dan een afwachtende houding met of zonder uitwendige kering rond 36 weken zwangerschapsduur.

## EPILOOG

Hopelijk nodigt dit proefschrift de lezer uit om aan de hand van diverse evidence-based conclusies tot inzicht te komen dat de TCG toegepast zou kunnen worden bij ziekten van deze tijd. Daarbij is, voor de validering van de TCG-behandelingen klinisch onderzoek noodzakelijk.

We hebben gezien dat het Nederlandse zorgstelsel ruimte voor aanvullende gezondheidszorg geeft. Opvallend is dat chronisch zieken zelf al op zoek gaan naar een aanvullende behandeling met acupunctuur. Een aantal zorgverzekeraars dekt inderdaad (gedeeltelijk) een dergelijke behandeling door middel van een aanvullende ziektekostenverzekering. De wereld van de medische wetenschap heeft de neiging de wenkbrauwen te fronsen bij deze praktijk van de complementaire behandeling met acupunctuur en moxa-therapie. De volgende vraag dringt zich op: 'gaat het hier om kwakzalverij of om een betrouwbare behandelingsmethode?' Het is de taak van de wetenschap om in het debat over de complementaire zorg nauwgezet aspecten van de complementaire zorg te bestuderen en de resultaten te publiceren. Naar mijn mening richt momenteel het huidige onderzoek naar complementaire geneeswijzen zich vrijwel uitsluitend op de strikt orthodoxe varianten

van complementaire gezondheidszorg. Er is geen twijfel dat de maatschappij zou moeten vechten - en nu ook al doet - tegen dergelijke praktijken. Maar geeft deze focus een getrouw beeld van wat bijvoorbeeld de rol van acupunctuur in de gezondheidszorg is? Als (complementair) zorgverlener denk ik dat het huis van de gezondheidszorg vele kamers kent. De complementaire zorg is een van die kleine kamers in dat huis. Maar dat blijft in het huidige onderzoek nog sterk onderbelicht.

Het valt me op dat het begrip 'complementaire gezondheidszorg' als onderdeel van de 'algemene gezondheidszorg' vaak wordt geassocieerd met een te late diagnosestelling en het daardoor mogelijk te laat adequaat behandelen van patiënten. Maar de doorsnee complementaire zorgverlener die hier leeft en werkt, is toch niet bepalend voor dat beeld. Integendeel, die associatie is er eerder een waarbij het bewijs van het gebrek aan integratie van complementaire zorgverleners gevonden wordt in crimineel gedrag van een 'kwakzalver met tunnelvisie'.

Ten slotte valt mij op dat de wetenschappelijke kennis en moderne evidence-based inzichten over complementaire zorg en de complementaire zorgverlenerwereld opvallend weinig aan bod komen in de meningsvorming van reguliere artsen en zorgverleners, politici en gezondheidseconomen, of althans zelden worden aangevoerd. Dat vind ik betreurenswaardig.

Met haar belofte van objectiviteit en waarheidsvinding mag de wetenschap in staat worden geacht om orde te brengen in dit debat. Omdat de wetenschap streeft naar objectieve resultaten en zoekt naar de waarheid, zou de wetenschap juist in staat moeten zijn om deze orde te brengen. Dit geldt in ieder geval voor de westerse wereld. Deze heeft immers een lange traditie van voldoende evidence-based onderzoek naar de effectiviteit en veiligheid van zorg, en is bereid om serieus de uitvoering van aanvullende zorg te overwegen.

Op dit moment blijkt echter dat de wetenschap zich toch niet voldoende actief bezighoudt met deze taak. Een goed voorbeeld is de lauwe ontvangst van het werk van toponderzoekers en wereldberoemde experts op het gebied van acupunctuur, zoals McPherson, Langevin, Pomeranz, Paterson, Hui, Kong en Ahn. Gebaseerd op jaren van evidence-based onderzoek zijn de resultaten van hun studies echte eye-openers om inzicht te verwerven over de werkingsmechanismen van de acupunctuur en mogelijkheden voor het gebruik van acupunctuur en moxa therapie. Zij concluderen een grote verscheidenheid van beschikbare toepassingen.

Dit alles overziend ben ik van mening dat wanneer uit kwalitatief goed epidemiologisch onderzoek blijkt dat acupunctuur even effectief en veilig is als andere werkzame therapieën, de implementatie van acupunctuur binnen de gezondheidszorg moet worden bevorderd. Acupunctuur zou meer krediet moeten krijgen dan momenteel het geval is. Ondanks publicaties in de peer reviewed tijdschriften, met inbegrip van de hoogwaardige tijdschriften als JAMA, Lancet, BMJ, en Pain, hebben de deskundigen deze bevindingen in de westerse gezondheidszorg nogal verwaarloosd. Dat zou een reden kunnen zijn waarom deze conclusies de politici en andere beleidsmakers nauwelijks hebben bereikt. Het doel van evidence-based onderzoek zou - naar mijn mening - moeten zijn dat bij positieve onderzoeksresultaten ook daadwerkelijk nagegaan wordt of de onderzochte interventies (als de acupunctuur en moxa-therapie) kunnen worden geïmplementeerd in de gezondheidszorg.

## AANBEVELINGEN

Gelukkig wordt onderzoek naar acupunctuur en moxa-therapie tegenwoordig steeds meer serieus genomen. De literatuur toont dit in vele klinische en epidemiologische disciplines aan. In Nederland is onderzoek naar de werkzaamheid van traditionele Chinese geneeswijzen in ontwikkeling. Met dit proefschrift, als eerste stap(steen), tonen we de meerwaarde van de onderzochte acupunctuur en moxa therapie aan op de verschillende gebieden van de gezondheidszorg. Het onderzoek naar de werking en effectiviteit van de TCG brengt vele professioneel werkende acupuncturisten in direct contact met de regulier geschoolde artsen met diverse specialismen. Ik vertrouw erop dat dit zal leiden tot meer erkenning, samenwerking en intervisie van elkaars capaciteiten.

De wetenschap heeft hier een opdracht en zou zich mede ten doel moeten stellen al die verschillende opvattingen over en inzichten in de (complementaire) zorgverlenerwereld - na onderzoek - over het voetlicht te brengen. Hierdoor wordt het maatschappelijk debat evenwichtiger.

Uit het onderzoek is gebleken dat acupunctuur en moxa-therapie aanvullende waarde hebben voor (chronisch) zieken en voor de preventieve zorg in de verloskunde. Daarnaast hebben we laten zien dat duiding van de menstruele cyclus, zoals die wordt gebruikt in de specifieke TCG-anamnese, de

sleutel zou kunnen zijn tot meer begrip in complex regionaal pijnsyndroom bij vrouwen.

Veiligheid is misschien wel het belangrijkste onderwerp in de gezondheidszorg. In dit proefschrift houden we een pleidooi voor een extra echo onderzoek bij zwangere vrouwen rond 30 weken zwangerschapsduur. Dit is in de eerste plaats vanwege de veiligheid van moeder en kind. In de tweede plaats heeft de echo rond de 30<sup>e</sup> week zwangerschap een sterk voorspellende waarde op de ligging van de foetus (stuit-, dwars- of hoofdligging) tijdens de bevalling. Daardoor is deze echo ook een objectief handvat om deze vrouwen bewezen effectieve (complementaire) therapieën aan te kunnen bieden en beter te begeleiden rond hun bevalling.

Veiligheid voor de patiënt is de verantwoordelijkheid van de praktiserend TCG therapeut of TCG-arts. Daar horen verplichtingen bij, zoals het lid zijn van een professionele organisatie. Deze staat dan garant voor de kwaliteit van de beroepsuitoefening door de leden en hanteert gedragsregels en regels betreffende ethiek, privacy en informatieverstrekking aan de patiënt, inclusief klacht- en tuchtrechtspraak. Daarnaast zijn de leden verplicht om jaarlijkse nascholingsdagen te volgen. De door de beroepsvereniging gestelde hoge eisen op het gebied van hygiëne, steriliteit en veiligheid tijdens de behandeling zijn vanzelfsprekend.

Het belang van deelname aan het maatschappelijk debat wordt niet altijd gezien als de 'core business' van de wetenschappers. Maar dat de wetenschappelijke kennis onvoldoende tot de politiek en de media doordringt, lijkt mij niet alleen een zaak van politici en journalisten, maar ook één die de wetenschap zich moet aantrekken. Wetenschappers hebben hier dan ook een maatschappelijke taak.

Chapter **10**

**Appendix**

- Glossary
- Abstracts of Chinese concepts in  
Traditional Chinese Medicine

## APPENDIX I

### Glossary

Acupuncture	In Standard Chinese, acupuncture is called 针灸 (zhēnbiān). The related word 针灸 (zhēnjiǔ) refers to acupuncture together with moxibustion [1].
AA	Acupuncture analgesia
Body-Inch system	Acupuncture points can be identified by anatomical markings such as eyebrows, hairlines or skin creases. The distance between points is not measured by a standard method because everyone's body is a different size. Instead, distances are measured by a metric called the "body inch," which equals the distance between the distal joint (the knuckle nearest the fingernail) and the middle joint of the middle finger. In Chinese: "cun" or "t-sun."
CAM	Complementary and Alternative Medicine
CSF	Cerebrospinal fluid, <i>Liquor cerebrospinalis</i> , continuously produced and absorbed, is a clear bodily fluid that occupies the subarachnoid space and the ventricular system within the brain and around the surface of the brain and spinal cord
DAOM	Doctorate program for TCM in the United States
De-Qi	"De-Qi" is the term used for the sensation felt when an acupuncturist reaches the level of "Qi" in the patient's body, and is the communication between patient and acupuncturist. De-Qi may feel like distention or an electrical impulse, sometimes radiating, in the area of the acupoint used. Once de-Qi has been reached, the acupuncturist will leave the needle in place and the sensation will fade [2]. De-Qi is not a necessary or integral aspect of acupuncture techniques.
EA	Electro acupuncture
EBM	Evidence-based medicine
Extracellular matrix	The extracellular matrix serves two main purposes. First, it prevents the immune system from triggering from the injury and responding with inflammation and scar tissue. Next, it facilitates the surrounding cells to repair the tissue instead of forming scar tissue.

FDA trials	Food and Drug Administration (FDA). Agency of the U.S. federal government authorized by Congress to inspect, test, approve, and set safety standards for foods and food additives, drugs, chemicals, cosmetics, and household and medical devices. ( <a href="http://www.britannica.com/EBchecked/topic/1498744/clinical-trial/292858/Clinical-trials-design">http://www.britannica.com/EBchecked/topic/1498744/clinical-trial/292858/Clinical-trials-design</a> )
GP	General Practitioner
IM	Integrative medicine.
LRP	Low resistance points
MDD	Medical Devices Directive, covers the regulatory requirements of the European Union for Medical Devices. Active implantable devices (e.g. pacemakers, implantable infusion pump) are covered by a separate directive, the Active Implantable Medical Devices Directive.
Moxibustion	Moxibustion works with acupuncture and the other modalities of TCM to restore balance and health to the body. Moxibustion and acupuncture are often of equal importance in treating many conditions, particularly in the most traditional practices. Moxibustion is the use of the herb mugwort ( <i>artemisia vulgaris</i> ), <i>moxa</i> in Chinese, to apply heat directly or indirectly to the body in order to warm body regions and acupuncture points, stimulate circulation, encourage a smooth flow of blood and qi, and protect against cold and dampness. Moxibustion is particularly effective in the treatment of chronic problems, "deficient conditions" (weakness), and in the treatment of the elderly.
mRNA	Is the template for protein synthesis; the form of RNA that carries information from DNA in the nucleus to the ribosome sites of protein synthesis in the cell
NAAV	<i>Nederlandse Artsen Acupunctuur Vereniging</i> ; <a href="http://www.naav.nl">www.naav.nl</a> .
Negative predictive value	The proportion of patients with negative test results who are correctly identified as <u>not</u> having the target disorder [3]. $NPV = \frac{\textit{specificity} * (1 - \textit{prevalence})}{(1 - \textit{sensitivity}) * \textit{prevalence} + \textit{specificity} * (1 - \textit{prevalence})}$



NVA	<i>Nederlandse Vereniging voor Acupunctuur</i> , <a href="http://www.acupunctuur.nl">www.acupunctuur.nl</a> . The NVA accredits six schools. Some of these schools accept students without any medical background. However, to join the NVA they must have been trained as a medic or paramedic training of four years or equivalent. The NVA accredits four courses for Chinese herbal medicine. The NVA is the only professional organization with an accreditation process, a curriculum and set standards.
NVTC	<i>Nederlandse vereniging voor Traditionele Chinese Geneeskunde</i> ; <a href="http://www.zhong.nl">www.zhong.nl</a> . Requires training in TCM similar to the NVA but used to require a less in-depth medical training than that required for paramedics. For that reason some insurance companies do not reimburse their members
Odds Ratio (OR)	The odds ratio is a way of comparing whether the probability of a certain event is the same for two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than one implies that the event is more likely in the first group. An odds ratio less than one implies that the event is less likely in the first group. <a href="http://www.cmh.edu/stats/definitions/or.htm">http://www.cmh.edu/stats/definitions/or.htm</a>
Placebo	An inert, or dummy, drug. Placebos are sometimes prescribed for maladies with no known scientific treatment or in cases in which an ailment has not yet been diagnosed. They are also used in tests involving responses to new drugs. In a blind test the patient does not know whether he or she is given the real drug or a placebo. In a double blind test neither the patient nor the physician knows.
Positive predictive value	The proportion of patients with positive test results who are correctly diagnosed as having the target disorder.[3] $PPV = \frac{\text{sensitivity} * \text{prevalence}}{\text{sensitivity} * \text{prevalence} + (1 - \text{specificity}) * (1 - \text{prevalence})}$
Pre-test probability	The probability of the target disorder before a diagnostic test result is known. $p(D+) = \frac{n(D+)}{n(D+) + n(D-)}$ , where n(D+) indicates the number of patients with the target disorder, n(D-) indicates the number of patients without the target disorder, and p(D+) is the probability of the target disorder.

Qi	Central to Taoist world view and practice is the concept of qi . Qi is life-force: that which animates the forms of the world. It is the vibratory nature of phenomena -- the flow and trembling that is happening continuously at molecular, atomic and sub-atomic levels. In China, the understanding of qi is inherent in the language. For instance: the literal translation of the Chinese character meaning "health" is "original qi." The literal translation of the character for "vitality" is "high quality qi." The literal translation of the character meaning "friendly" is "peaceful qi."
Qi Gong	A method of breathing and movement to improve the body energy and prevention of disease.
RCT	Randomized Controlled Trial
Sensitivity	The fraction of people with the disease that the test correctly identifies as positive.
Sham, minimal or placebo acupuncture	Acupuncture needles are inserted randomly and less deeply around the painful area while avoiding the meridians.
Specificity	The fraction of people without the disease that the test correctly identifies as negative.
Tai Chi	A slow movement exercise to strengthen the body and maintain good bodily functions.
TCM	Traditional Chinese Medicine
Translational research:	Translational research, with its focus on removing barriers to multi-disciplinary collaboration, has the potential to drive the advancement of applied science. An attempt to bridge these barriers has been undertaken particularly in the medical domain where the term translational medical science has been applied to a research approach that seeks to move "from bench to bedside".
Verum acupuncture	In verum acupuncture, needles are inserted up to 1-1/2 inches (4 cm) deep at "meridians" and other prescribed locations until the patient is said to experience a numbing sensation, called 'De-Qi'.
WHO	World Health Organization

Yin / Yang

The traditional works "Treatise on Febrile Diseases" and "The Yellow Emperor's Classic" consider yang as positive and yin as negative. Yang people react to disease in an aggressive, active, progressive, and warm way. For example, if a yang person has a cold, his pulse speeds up, temperature rises, face reddens, throat becomes sore, body pain intensifies, and thirst occurs. Contrarily, yin people react to disease in a negative, passive, cool way. If a yin person - the very old and very young in particular - contracts an acute upper respiratory infection, he or she loses energy and develops a yellowish complexion and a slow, weak pulse; usually there is no fever or coughing. Although they seem healthy, yin people are resistant to cure and require extensive therapy. A Chinese doctor prescribes tonics for yin problems and sweating agents or antipyretics for yang problems.

## APPENDIX 2

### Abstracts of Chinese concepts in TCM

Qi



According to Chinese thinking, an entity called Qi is in existence in the greater world (universe) and in the lesser world (human being) (1). Like the ancient Greek concept "pneuma", qi is a sustaining life force that neither can be seen nor measured. Qi, blood and body fluids are fundamental substances in the human body to sustain normal vital activities as well as carrying out the physiological functions of the organs, tissues and meridians. Generally speaking the word Qi relates to both substance and function. The Chinese distinguish between the inner and the outer Qi. The inner Qi is the life energy in a living body. The outer Qi relates to the weather and the air. The inner Qi has three main functions: the Ying Qi is to nourish the body, the Wei Qi is to protect the body, and the Qi is to move around and to put energy in action wherever it is needed. The inner Qi derives its energy from food, water and air. The inner and outer Qi can communicate through one's respiratory system, which is vital for life. The relation between Qi and health is discussed extensively in the canonical textbook Huang Ti Nei Ching ( Inner Classic of the Yellow Emperor) (2): 'Health is the harmonious, uninterrupted flow of Qi, made possibly by the perfect balance between Yin and Yang. Disease will ensue when the Qi not flows'. Transmission of this energy from side to side, top to bottom and from the inside to the outside of the body – and thus reaching balance – is of great importance for a person's health.

In acupuncture, needling at specific points modifies the underlying Qi, affecting inner organs, pain perception, and inflammatory processes. When the Qi is stimulated or tempered, sensations such as tingling, heaviness, soreness, and pressure may or should occur ("de-Qi", (3)).

Each meridian corresponds to an organ or organ system (4, 5).

The ultimate goal of the TCM practitioner is to restore and maintain a balanced state of Qi in the individual.

Factors that can affect Qi flow include personal emotional states such as anxiety, stress, anger, fear or grief, or physical conditions such as poor nu-

trition, weather conditions, hereditary factors, infection and trauma. Also failure to develop emotionally in the various stages of life can be seen as stagnation, to be restored by acupuncture or other TCM-treatments.

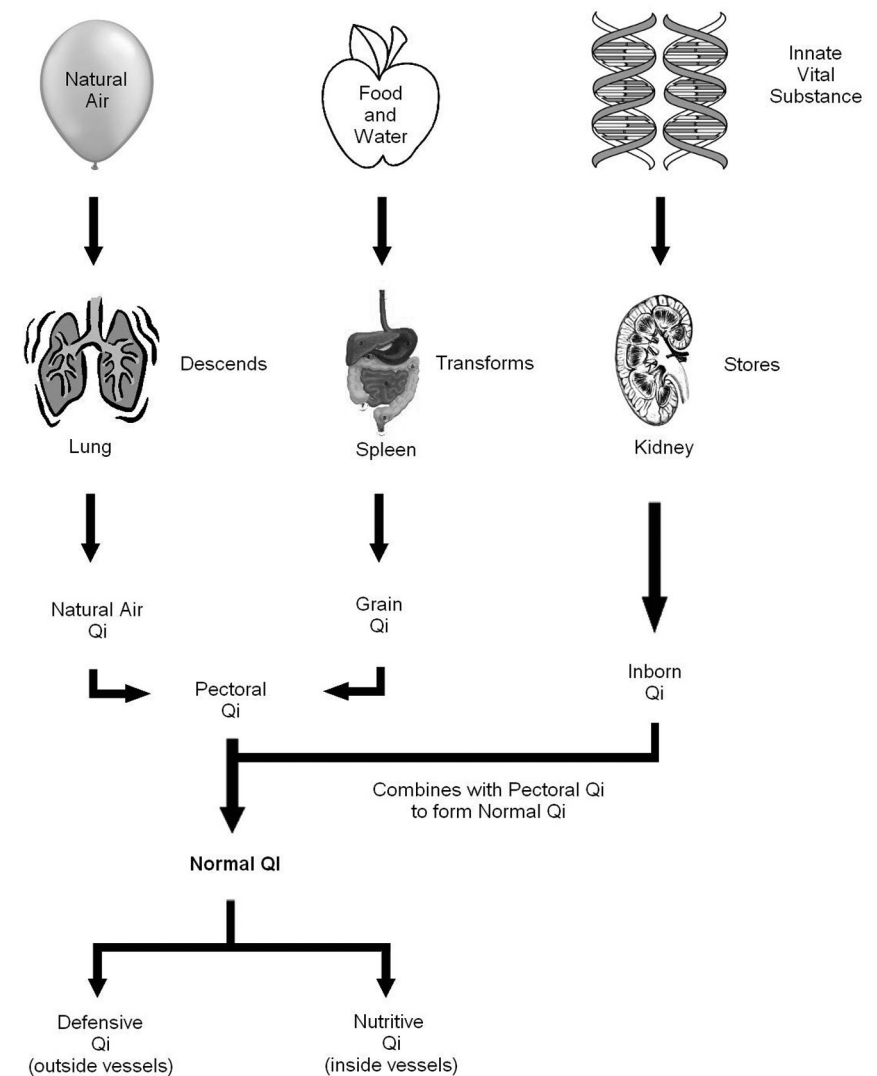
The aspects of life that are touched by acupuncture include complex functions common to all levels of evolution, including microcirculation and immune function, etc. Acupuncture can also restore dysfunctions such as sleep disturbances and menstrual cycle problems, which sometimes may occur even quite some time after the actual initiating trauma or disease (Figure 1). Many modalities of acupuncture make use of various forms of physical stimulations (pressure, heat, sound, electricity and (laser) light) to achieve that the body can interact with these field energies effectively and at advantage. The field concept is equivalent to the Qi concept (1). In Western science, only physicists and mathematicians have a real feel about these 'nothings' and 'non-sense' (invisible and untouchable). Worldwide a variety of approaches to acupuncture therapy have been developed. But this variety does not suggest that one is better than the others. Evidence based results should help stimulate both the dialogue and research amongst practitioners and Western doctors.

### Yin and Yang

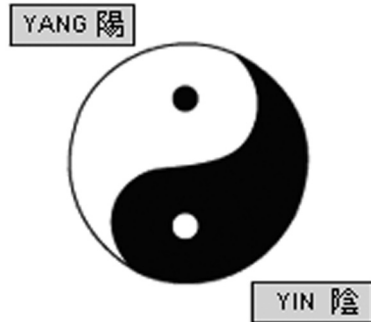
The Chinese expressed the Qi concept using their doctrine of Yin and Yang, in which everything is an amalgam of two opposites. Yin is associated with physical substance, water, blood, the dark side of the hill or the female principle. Yang is associated with activity, fire, Qi, the sunny side of a hill or the male principle. They complement one another and may explain relationships between dynamic interactions in the human body. Therefore, the guiding rule to cure disease is to regulate or harmonize the Yin and Yang in the body so as to restore balance again.

The Yin-Yang balance was considered to be constantly dynamic and fluctuating, striving to 'a perfect and dynamic balance'. If one was out of balance, in an energetic sense, the treatment principle would be to re-establish that balance. The Yin-Yang balance is inherently built into our bodies, such as acid- vs. base (pH in body fluid), sympathetic vs. parasympathetic, or adrenergic vs. cholinergic. Western medicine has yet to appreciate this principle of treating the human body as a system. In Western medicine, system biology, researched and described by Jan van der Greef, departs from this point of view (6).

**Figure 1.** The proper quality, distribution and flow of Qi is of extreme importance in health.



**Figure 2.** Modern symbol of Yin and Yang, the concept of opposing unities.



Yin /Yang is the Dao of Heaven/Earth  
 The common thread in the 10,000 Beings  
 The father and mother of change and transformation  
 The root and beginning of life and death...  
 To cure illness one must search the root

Yin and Yang are neither materials nor energy. TCM is an area where the Yin-Yang theory is used to understand complicated health relationships in the body.

**The Ching-Luo Doctrine: the meridians**

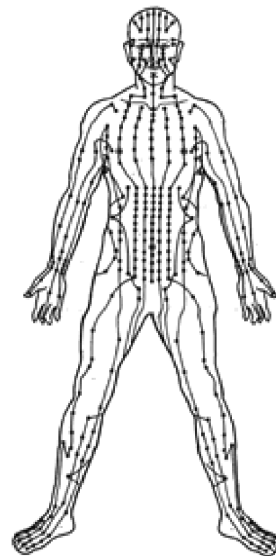
Along with the notion of Qi, TCM recognizes a subtle energy system by which Qi is circulating through the body in a network of channels or 'meridians' (Figure 3)

The Ching-Luo (the meridians) have the following functions:

- To guide the flow of blood and Qi (life energy)
- To harmonize Yin and Yang
- To animate the muscle and bone
- To ease the joints

They serve as the energy transmission channels running between the internal organs and between the interior and exterior of the body. This communication function can bring the message of illness to the surface, and thus facilitates making a diagnosis and treating the disease through actions on the surface. The meridians apparently have many features quite similar or parallel to the sympathetic and para sympathetic nerves.

**Figure 3.**

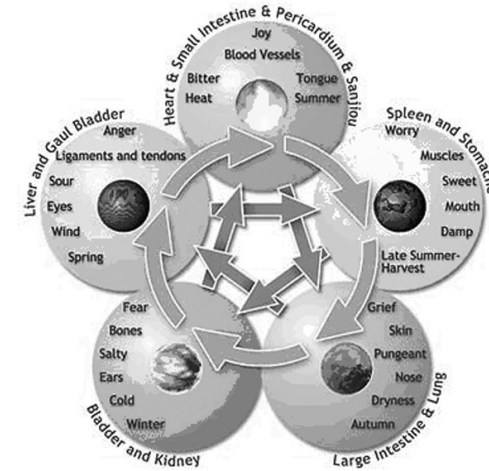


**The Wu-Hsing Dynamic Model**

The Wu-Hsing Dynamic Model first appeared in the Su Ching (about 1000 B.C.). Hsing in Chinese means motion, action and interaction, and Wu means five. It is therefore also (wrongly) referred to as five-element system (water, fire, wood, metal and earth). It is a dynamic model applied to the organic system of humans that establishes their mutual relationships in a systemic way. Confucius' writings about morality (1000 BC) served as a foundation for Chinese education, and this model. He derived five cardinal relationships: between ruler and ruled, between husband and wife, parents and children, older and younger brothers and fiend and friend. The rigorous adherence of those relationships yielded harmony and balance. In medicine, this model can provide useful guidance through the five cardinal relationships, both in diagnosis and in therapy.

Many 'laws' and treatment principles such as Yin-Yang laws and the Wu-Hsing Dynamic Model are not philosophical concepts but rather scientific deductions from long observations of system operations, and described in scientific studies (Figure 4).

**Figure 4.** Five elements



**Yin-Qi & Yang-Qi Give Birth to the Five Elements:**

According to Taoist cosmology, Yin-Qi and Yang-Qi – the primordial feminine and masculine energies – produce what are known as the “Five Elements.” These, in turn, give birth to the “ten-thousand things,” i.e. all of manifest existence. The Five Elements are Wood, Fire, Earth, Metal and Water. (<http://www.tuina.com.au/5-elements.html>)

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Chapter



**Contributing authors**

**List of publications and presentations**

**PhD portfolio**

**Dankwoord**

**About the author**

## CONTRIBUTING AUTHORS

### **L.R. Arends, PhD,**

Department of Biostatistics, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands,

And:

Institute of Psychology, Erasmus University Rotterdam, Rotterdam the Netherlands

### **J.L. Bosch, PhD,**

Department of Epidemiology and Radiology, Erasmus University Medical Center Rotterdam, The Netherlands

### **I. Bouman, BSc,**

The Rotterdam Institution for Training Midwives, Rotterdam, The Netherlands

### **H. van Brero, BSc,**

Clinic for Acupuncture and Physical Therapy, Zandvoort, The Netherlands

### **J.J. Duvekot, MD, PhD,**

Department of Obstetrics and Gynecology, Division of Obstetrics and Prenatal Medicine, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands

### **Prof. M.G.M. Hunink, MD, PhD,**

Program for Assessment of Radiological Technology  
Department of Epidemiology, and Radiology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

And:

Department of Health Policy and Management, Harvard, School of Public Health, Boston, USA

### **Prof. F.J.P.M. Huygen, MD, PhD,**

Department of Anesthesiology, Erasmus Medical Centre, Rotterdam, The Netherlands

### **B. Jacobs, MSc, BSc,**

The Rotterdam Institution for Training Midwives, Rotterdam, The Netherlands

### **V.W.V. Jaddoe, MD, PhD,**

The Generation R Study Group, Erasmus University Medical Center, Sophia Children's Hospital Rotterdam, the Netherlands

And:

Department of Epidemiology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

### **A.C.J.W. Janssens, PhD,**

Department of Epidemiology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

### **G.C. Kaandorp, MSc.**

Department of Epidemiology and Biostatistics, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

### **Prof. J. Klein, MD, PhD,**

Department of Anesthesiology, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands

### **Y.S. Liem, MD, PhD,**

Department of Epidemiology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

### **Prof. E.A.P. Steegers, MD, PhD,**

Department of Obstetrics and Gynecology, Division of Obstetrics and Prenatal Medicine, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands

And:

The Generation R Study Group, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, the Netherlands

### **K.T. Tan, MD,**

Unipolis, Amsterdam, The Netherlands



**L. Tan, MD,**

Department of Epidemiology,  
Erasmus University Medical Center Rotterdam,  
Rotterdam, The Netherlands

**F. Wesseldijk, MD. PhD,**

Department of Anesthesiology, Erasmus Medical  
Centre, Rotterdam, The Netherlands

**F.J. Zijlstra, PhD,**

Department of Anesthesiology, Erasmus Medical  
Centre, Rotterdam, The Netherlands

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- *Abstract and poster presentation:* Cost-effectiveness of Breech Version by Acumoxa for women with a breech foetus at 33 weeks gestation: a modelling approach. I. van den Berg, G. C. Kaandorp, J. L. Bosch, J. J. Duvekot, L. R. Arends, M.G. M. Hunink. Poster presentation 2nd European Conference for Integrative Medicine, Berlin - November 20 - 21, 2009
- *Abstract and poster presentation:* I. van den Berg, G. Kaandorp, J.L. Bosch, W. Hop, J.J. Duvekot, M.G.M. Hunink. Fewer Caesarean sections with the aid of Breech-version Acumoxa: Decision analysis of effectiveness and cost. Annual Conference of the society for Acupuncture Research 10 Years post-NIH Consensus Conference, Baltimore, USA 2008

- *Abstract and oral presentation:* van den Berg - de Lange I, Wesseldijk F, Zijlstra FJ, Menstrual Cycle Disorders: Indication of Predisposition in Development of Complex Regional Pain Syndrome I?, 14 th Annual Symposium on Complementary Health Care, London, UK, 2007, FACT
- *Abstract and oral presentation:* I. van den Berg, G. Kaandorp, J.L. Bosch, W. Hop, J.J. Duvekot, M.G.M. Hunink. The effectiveness and cost-effectiveness of Breech Version Acumoxa compared to standard care to correct breech presentation, 13 th Annual Symposium on Complementary Health Care, Exeter, UK, 2006, FACT
- *Abstract and oral presentation:* I. van den Berg, B.Jacobs, I. Bouman, J.L. Bosch, M.G.M. Hunink, Effectiveness of acupuncture-type interventions to resolve breech presentation compared to expectative policy, a meta-analysis, 12 th Annual Symposium on Complementary Health Care, Exeter, UK, 2005, FACT
- *Abstract and oral presentation:* van den Berg-de Lange I, Wesseldijk F, Niehof S, Huygen FJPM, Zijlstra FJ Registration of effects after acupuncture in complex regional pain syndrome by computer-assisted video thermography. 10 th Annual Symposium on Complementary Health Care, London, UK, 2003, FACT

### Invited presentations

- 7<sup>th</sup> World congress of Chinese Medicine 2010, 1-2 October 2010, The Hague, The Netherlands
- International Acupuncture Congress, 19./20. September 2009, Olten, Switzerland. *Presentation of the Dutch translation of the booklet: Natural pain relief techniques for childbirth using acupressure; promoting a natural labour and partner involvement.* COPYRIGHT Debra Betts 2003 ©. ISBN 0-473-04467-6
- ETCMA SYMPOSIUM March 2009: Research: What, How and for Whom? Zurich, Switzerland, 2009
- NAAV, December 8, 2007, Bunnik, The Netherlands
- Acupuncture and Science. Jubilee congress 30 years NVA, March 14, 2007, Ermelo, The Netherlands
- Chronic CRPS and acupuncture: a new approach. Symposium Integration of Eastern & Western Medicine, 2006, Amsterdam, The Netherlands

- Effectiveness of acupuncture-type interventions to resolve breech presentation compared to expectative policy, a meta-analysis, Symposium Integration of Eastern & Western Medicine, 2006, Amsterdam, The Netherlands

## PHD PORTFOLIO

Name PhD student: Clasina (Ineke) van den Berg – de Lange  
 Erasmus MC Department: Radiology and Epidemiology  
 Research School: Netherlands Institute for Health Sciences (NIHES)  
 PhD period: 2004-2010  
 Promotor: Prof. dr. M.G.M. Hunink  
 Co-promotor: Dr. J.J. Duvekot

### I. PhD training

#### General academic skills

- Introduction to Medical Writing, NIHES, Rotterdam, 2003
- Introduction to Statistical Software, NIHES, Rotterdam, 2004

#### Research skills

MSc in Clinical Epidemiology, NIHES, Rotterdam, 2002-2004 (total study workload of approximately 120 ECTS): various courses in research methodology, including: Principles of Research in Medicine and Epidemiology, Study Design, Clinical Decision Analysis, Advanced Medical Decision Analysis, Introduction to Data-analysis, Regression Analysis, Topics in Evidence-based Medicine, Meta-analysis, Advanced Course on Diagnostic Research.

#### Postdoctoral training, since 2000

In-depth courses  
 TCM: Practical Shāng Hǎn Lùn Diploma Course, 2010  
 Course mindfulness, 2010  
 Course Scientific English (4 ECT)  
 Traineeship transposition Therapy mrs. Shinka, Macedonia, 2003  
 Traineeship in International Trainingscentre of Dongzhimen Hospital, Beijing, China, 2001  
 Nei Jia Stems & Branches Course, The Anglo Dutch institute for oriental medicine, Overveen, the Netherlands. 2000  
 Psychopunctuur Basic Emotional Structuring Test (BEST) Dr. Med. H. Calehr. 1995-2001

#### Academic and professional activities

- 2003-present Member of weekly ART (Assessment of Radiological Technologies) meeting  
 National and international conferences Attended
- London. Integrated Care and the management of Chronic illness: the Patient's agenda for healthy living, 2009.
  - the Kennispoort verloskunde conferentie 2008, 2009
  - Annual Meeting of The Dutch Association for Acupuncture (Utrecht, Netherlands) in 2004, 2005, 2006, 2007, 2008, and 2009
  - Congres Supplement Plus, 2009

#### Travel grants

- The Dutch Association for Acupuncture (N.V.A.)

#### Teaching activities since 2000

- 2009-2010 Developed the Minor: Inleiding Evidence based Integratieve Geneeskunde  
 2009-2010 Teaching 4<sup>th</sup> year medical students during their VO4, Erasmus MC,  
 2005-2007 Visiting teacher Rijksuniversiteit Groningen (RUG), Complimentary Medicine, Groningen, the Netherlands  
 2005-2007 Teacher Acupuncture and Chinese Herbal Medicine (The Anglo Dutch institute for oriental medicine, Supervisor research projects, Overveen, the Netherlands  
 1986-2005 Teacher, professional training Meer Bewegen voor Ouderen, Sportraad Zuid-Holland, 's Gravenhage, the Netherlands

#### Supervising research projects of BSc and MSc students

- 2010 Christel Romeijn, Genesis Kozdras, and Wierin Binda  
 Medical Sciences: Elective course 3rd year, Department of Obstetrics & Gynaecology  
*Title:* 'Factors associated with non-vertex position of the singleton fetus at term'

- 2009 Marielle Kornet, and Marieke de Kruijf, The Rotterdam Institution for Training Midwives, Rotterdam, The Netherlands.  
*Title:* “Is het verminderen van een zwangerschapsdepressie met behulp van acupunctuur mogelijk, om het maternale sterftcijfer te verlagen”
- 2009 Joyce Vaandrager, and Jantine Buxbaum, The Rotterdam Institution for Training Midwives, Rotterdam, The Netherlands  
*Title:* NIET-medicamenteuze aanpak pijnbehandeling tijdens de baring bij laagrisico zwangeren: evidence based practice in NL
- 2008 Loek Tan, Master of Science Degree (Medical Sciences), Erasmus University Rotterdam, the Netherlands  
*Title:* Health-related quality of life in patients with musculoskeletal complaints in a general acupuncture practice: an observational study.
- 2006 Josine Simons, Academy for Physiotherapy “Thim van der Laan” Nieuwegein, The Netherlands.  
*Title:* Developmental Coordination Disorder - Mijn kind is ‘onhandig’. Een multidisciplinaire aanpak bij kinderen met DCD.
- 2005 Ben Jacobs, and Irene Bouman, The Rotterdam Institution for Training Midwives, Rotterdam, The Netherlands.  
*Title:* Systematic review of the use of moxibustion for correction of breech presentation
- 2004 Marijke Moes, and Barbara van Gelderen, Hogeschool Rotterdam department Physiotherapy, Rotterdam, The Netherlands.  
*Title:* The Possible Relation between Menstrual Disorders and Predisposition to CRPS I

## DANKWOORD

*'Als je ergens weinig van weet is er maar één manier: in die wereld stappen'*

Het tot stand komen van een proefschrift gaat niet vanzelf. Een proefschrift is een leesbare getuige van het groeiproces dat je als wetenschappelijk onderzoeker doormaakt. Er zijn ongelofelijk veel mensen die mij de afgelopen jaren hierbij enorm hebben geholpen. Bij dezen dank ik iedereen hartelijk die aan dit proefschrift heeft meegewerkt. Een aantal mensen bedank ik graag in het bijzonder.

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*'Als je wilt dat je droom uitkomt, moet je stoppen met dromen'*

*(Josephine Baker)*

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*'Zelfs een mars van duizend mijl begint met de eerste stap.'*

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'Follow your passions, but do not put all your eggs in one basket!'

## ABOUT THE AUTHOR

Ineke van den Berg-de Lange was born on May 5<sup>th</sup>, 1955 in Enschede, the Netherlands. She graduated from the Haags Montessori Lyceum, HBS-b in The Hague, in 1973. That same year she started her study physical therapy at the SUPA in Utrecht. In 1978 she graduated and started to work as a physical therapist in Capelle aan den IJssel, and moved to Berkel en Rodenrijs in 1978. In 1983 she founded 'Rodenrijs', her own private clinic for physical therapy and Complementary Medicine.

Alongside to the physical therapy Van den Berg practices as an acupuncturist, shiatsu therapist and herbalist for more than 30 years, with a special interest in obstetrical problems and complex pain disorders as CRPS type I. In 2002, next to her work in her own clinic, she started as researcher at the Erasmus Medical Center, joining the Pain Treatment Center, under supervision of Prof. Dr. Jan Klein and Prof. Dr. Frank Huygen. In 2003 she entered as researcher at the department of Epidemiology and Radiology of the Erasmus University MC, Rotterdam, supervised by Prof. Dr. Myriam Hunink which research resulted in this dissertation. Van den Berg obtained a Master's Degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES) in Rotterdam in 2004. Part of the research presented in this dissertation was performed under supervision of Dr. J.J. Duvekot at the department of Obstetrics and Gynecology.

Ineke van den Berg is married to Jelle van den Berg and they have two daughters, Roos and Anouk, and a son, Wouter.