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Enhancing Positive Mood in Older Adults:

Implications for Vaccine Effectiveness

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Abstract

The influenza vaccine is less effective in older adults compared to their younger counterparts. At the same time, this population is more susceptible to contracting influenza, with more severe consequences, including higher rates of complications, hospitalisations, and deaths. There is an abundance of evidence demonstrating how psychological factors, such as stress, can influence and modulate immune function, including response to vaccinations. Recent work has extended this to other psychological factors, suggesting that mood, or affect, may also be linked to vaccine response, however the evidence here is much more limited. This thesis presents three inter-related pieces of research, which sought to build on this evidence base and contribute to our current understanding of the influence of mood on vaccinations. The ultimate aim of this research was to develop an intervention to enhance positive mood, with a view to enhancing the effectiveness of the influenza vaccination in the older adult population.

First, the evidence surrounding the effectiveness of using participant-driven choice in interventions compared to 'no-choice' interventions was systematically reviewed. This review sought to investigate whether the integration of participant choice within an existing, previously trialled, positive mood intervention would maximise mood enhancement and thus the potential to enhance vaccine-specific antibody levels. The review found that whilst choice-interventions led to less drop-out and greater adherence, evidence for mood-related outcomes was unclear and warranted further investigation.

Second, a randomised controlled clinical study (n=654) was conducted to investigate the effectiveness of the previously trialled fixed-content positive mood intervention, a new choice-based intervention, and usual care, in terms of enhancing positive mood. Vaccine response at four-weeks post-vaccination was assessed as a secondary outcome. Results showed that both the fixed-content and choice-based interventions significantly improved mood compared to usual care, however there were no significant differences between the two interventions. There were no significant differences between groups in terms of antibody levels at four weeks post-vaccination.

Finally, a qualitative study using a thematic-content hybrid analysis approach was carried out with a selection of participants from the randomised trial, to assess participants' perceptions of how the intervention may or may not have worked, and to identify ways in which both the intervention and study experience as a whole could be improved for a future trial implementing the optimised intervention. Analysis revealed that both interventions, as well as the overall study experience, were liked by participants, indicating that further optimisation may not be necessary. Additionally, several potential mechanisms underlying the relationship between the interventions and mood were identified.

The research presented in this thesis has several important implications. Firstly, that the use of choice should be considered where there is concern regarding drop-out or adherence, but may not be more effective than no-choice interventions in enhancing mood. Secondly, that brief positive mood interventions are effective in enhancing positive mood in older adults in a

primary care setting. Future work is required to evaluate their impact on immune outcomes including mechanistic work to understand the relationship between mood and immunity, and a large scale trial, with immune response as the primary outcome.

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1.1 Chapter overview

Infectious diseases constitute a significant global problem both socially and economically (Fonkwo, 2008; Larson, 1997). Vaccines represent one of the most effective and safe ways in which to protect individuals from more than 26 of these infectious diseases (Andre et al., 2008; World Health Organization, 2019). This chapter seeks to provide the context of this thesis, by discussing why influenza vaccination in the elderly is both problematic and necessary. It will do this firstly by introducing the problem of infectious diseases and the contribution that vaccination has made in combatting them. In doing so, this chapter will outline the role of the immune system in vaccination and examine both innate but particularly adaptive immunity, and the immune processes on which vaccines rely. The next part of the chapter will focus specifically on influenza, a common infectious disease costing the NHS millions of pounds each year (National Institute for Health and Care Excellence, 2017, 2018). This section will describe influenza, the types of influenza vaccines available, and discuss the benefits and limitations of influenza vaccination. In particular, this section will focus on populations in which the influenza vaccine is less effective and will introduce the concept of immunosenescence.

1.2 Infectious diseases

Of the top 10 causes of death worldwide in 2016, three were communicable diseases, with lower respiratory tract infections the most deadly, responsible for three million deaths (World Health Organization, 2018c). Diarrhoel diseases and tuberculosis were the ninth and tenth top global causes respectively, jointly accounting for 2.7 million deaths. Although these figures

represent a decrease in the number of deaths from communicable diseases since 2010 (World Health Organization, 2018c), they still account for a significant number of deaths each year.

Infectious diseases are caused by pathogens, which are bacteria, viruses, fungi or parasites (Murphy & Weaver, 2016). They cause disease by damaging or disrupting cells in the body. Different types of organisms attack the body in different ways. For instance, viruses are able to hijack cells to produce copies of the virus. This can lead to cell death through cell lysis (the breaking down of a cell that compromises its integrity) or apoptosis (a form of programmed cell death) (Kaminskyy & Zhivotovsky, 2010; Roulston, Marcellus, & Branton, 1999). Bacteria can also rapidly multiply to overcrowd the tissue and disrupt normal function, and some produce toxins which can paralyze cells (Drexler, 2010).

There are several ways to reduce an individuals' risk of contracting an infectious disease. For instance, infection control behaviours, including handwashing, covering coughs and sneezes to reduce their reach, keeping surfaces clean, only drinking clean water, and not sharing food or drink with others may all help to reduce disease transmission (Centers for Disease Control and Prevention, 2010, 2011; Grayson et al., 2009). However, by far one of the most effective ways to minimise risk of contracting an infectious disease is to be vaccinated (Centers for Disease Control and Prevention, 2018c; Muller CP, 2007; Nichol & Treanor, 2006).

1.3 Vaccines and their role in combatting infectious disease

Every year vaccinations prevent 2-3 million deaths from 26 vaccine-preventable diseases (World Health Organization, 2018a). The World Health Organisation (WHO) describes vaccinations as one of the greatest contributions to reducing the burden of infectious diseases, second only to the provision of clean water (Andre et al., 2008). Vaccines have contributed to the near worldwide eradication of some diseases, most notably smallpox, with the last known case in 1977, and its official eradication in 1980. The development of the diphtheria vaccination has seen cases of diphtheria reduce from over 350,000 new cases each year before the vaccine, to fewer than five cases per year, since vaccination became widespread (Sompayrac, 2019). Polio has been eliminated in all but three countries, and 85% of infants worldwide have now been vaccinated against diphtheria, tetanus, and pertussis (DTP) (World Health Organization, 2018a). In the UK, whooping cough has reduced from approximately 120,000 cases before the 1950's, to less than 1500 cases per year between 2000 and 2011 (NHS, 2016). Meningitis C has also almost been eliminated in the UK, with just two deaths between mid-2011 to mid-2012, seeing a 99% reduction in cases since the vaccines was introduced in the UK in 1999 (NHS, 2016).

Vaccines not only provide an individual with immunity to a specific disease, but they can also provide indirect protection for a population, thereby reducing its transmission through a mechanism called herd immunity. Herd immunity is defined as the resistance to the spread of disease as a result of a sufficiently high level of immunity in a population (Desai & Majumder, 2020; Fox, Elveback, Scott, Gatewood, & Ackerman, 1971). For herd immunity to be effective, a very high proportion of people need to be vaccinated. Although

this varies depending on the contagiousness of the specific disease, it usually means that at least 80% of the population need to be vaccinated (Centers for Disease Control and Prevention, 2014; John & Samuel, 2000; The University of Oxford, 2018). Therefore, higher vaccination rates reduce the opportunity for disease spread, which in turn protects those who may be particularly vulnerable to infection. For instance, although new-born babies are immune to many diseases due to protection from their mothers, this immunity is lost during the first year of life. This means that very young children may be more likely to become ill if exposed to a pathogen before they have been vaccinated. Other vulnerable populations include those who are unable to receive a vaccination due to medical reasons, or those who don't respond to a particular vaccination (Centers for Disease Control and Prevention, 2017b).

1.4 How vaccines work

To understand how vaccines work, first it is necessary to understand the fundamentals of the immune system. This next section will briefly describe the components of the immune system and the role the immune system plays in fighting infectious disease more broadly, before focusing specifically on the role of the immune system in vaccination.

1.4.1 *The immune system*

The immune system consists of a set of organs, cells, chemicals and proteins that collectively seek to protect the body from pathogens. Different types of pathogens vary in their size and function; therefore, the immune system needs to have a range of defence mechanisms in order to effectively protect the body. The body has several initial lines of defence to stop an intruding

pathogen, including both physical barriers such as skin and hair, and chemical barriers such as stomach acid and mucus. When a pathogen manages to evade these defences and enter the blood stream or tissues (e.g., through a cut, bite or inhalation), a range of molecular and cellular components of the immune system are present to help protect the host.

1.4.1.1 Innate immune response

To protect the body from a pathogen that has entered the tissue, first the immune system needs to recognise the pathogen by locating and identifying it, and then defend against the pathogen by repelling or destroying it. There are two stages of immune response that are involved in this process. The innate immune response (sometimes referred to as natural immunity) is a rapid response that takes place over a period of seconds or hours (Porcelli, 2017). However, it is also non-specific, meaning that although the cells can recognise that a pathogen has entered the body, they cannot determine what type of pathogen it is, and therefore cannot launch the most specific and effective attack and is only moderately efficient at clearing an infection (Todd, Spickett, & Fairclough, 2015). They are also unable to determine if the pathogen is novel or has been previously encountered, therefore this response does not vary according to previous experience. The innate response involves a number of cells and proteins, including macrophages, dendritic cells, mast cells, neutrophils and complement, each of which will be described in more detail. The innate immune response begins with the recognition of the pathogen by cells such as macrophages and dendritic cells (Ozinsky et al., 2000), which constantly test their environment and have the ability to distinguish between ‘foreign’ and ‘self’ molecules (Delves & Roitt, 2000). Therefore, as soon as a pathogen enters the tissue, the macrophage

or dendritic cell will recognise its presence. Macrophages have several functions once they have recognised an invading pathogen. They can kill pathogens by a process called phagocytosis, in which the pathogen is engulfed and eradicated. Macrophages also trigger other cells, such as mast cells, to produce an inflammatory response, and activate and recruit cells such as neutrophils to the immune response (Janeway, Travers, Walport, & Shlomchik, 2001). Once activated, these neutrophils can also kill cells through phagocytosis as well as bactericidal mechanisms. This sequence of events can also be triggered by suite of proteins called complement, which binds to the pathogen to aid in macrophage recognition, and also activates mast cells and neutrophils. Dendritic cells are also involved in the innate immune response. Like macrophages, dendritic cells also test their local environment. However rather than kill the pathogen by phagocytosis, once the dendritic cell recognises the pathogen, it ingests, processes, and presents protein sequences from the pathogen called antigens (Banchereau & Steinman, 1998). Antigens are bound to the surface of a pathogen and are unique to the specific pathogen. Dendritic cells then migrate to local immune organs and lymph nodes, to present the antigens to cells of the adaptive immune response. This action is the bridge between the innate and adaptive immune response.

1.4.1.2 Adaptive immune response

The adaptive immune system response (also known as specific immunity) is slower, taking several days or weeks to develop, but unlike the innate response, this adaptive response is highly specific, making it extremely effective at clearing pathogens (Delves & Roitt, 2000). The involvement of the adaptive response begins once antigen presenting cells, most commonly

dendritic cells, take the antigen to the lymph nodes. Once in the lymph nodes, the antigen presenting cells encounter naïve T and B cells and present the antigens, which act as information about the pathogen. T and B cells have receptors, which recognise specific antigens. The body produces a vast amount of T and B cells all with different receptors so that when a specific pathogen enters the body, it should be recognised by the correct specific receptor. For instance, an adult human will have between 100 and 300 billion naïve T cells and 3 billion naïve B cells, with an estimated frequency of T and B cells for any specific antigen between $1:10^4$ and $1:10^6$ (Bains, Antia, Callard, & Yates, 2009; Dong & Markovic, 2018; Sompayrac, 2019; Todd et al., 2015).

When a dendritic cell presents a pathogen antigen to a naïve T cell with the specific receptors for that antigen, they bind and the T cell becomes activated. Once activated, the T cell can divide, proliferate and differentiate to effector T cells (Parkin & Cohen, 2001). There are two types of effector T cells, which differ in their function (Parkin & Cohen, 2001). Killer T cells (also known as CD8 or cytotoxic T cells), kill virus-infected cells through a process called apoptosis, which prevents pathogen replication and releases infectious bacteria or virus particles from the infected cell (Murphy & Weaver, 2016; Parham, 2014). Helper T cells (or CD4 cells) do not directly attack the pathogen but can help other cells to do so by releasing cytokines (Sompayrac, 2019). Cytokines are small protein molecules, which are important for communication via cell signalling. For instance, T helper 1 (T_H1) releases cytokines that are particularly helpful for eradicating infectious microbes such as viruses or bacteria. T_H1 cytokines also help with the proliferation of killer T cells, and the continued activation of macrophages, as well as influencing B cell production of specific antibodies (Murphy & Weaver, 2016; Sompayrac,

2019). T Helper 2 (T_H2) cells control infections caused by parasites or pathogenic infections. T_H2 cytokines help by stimulating the proliferation of helper T cells, encouraging B cells to proliferate and to produce antibodies, and to produce intestinal mucus which is helpful in the prevention of intestinal parasites (Sompayrac, 2019).

B cells are also activated in the lymph nodes. There are multiple ways in which B cells can become activated, however most commonly this occurs by the presentation of antigens by dendritic cells that engages the specific antigen receptors of the naïve B cells, alongside stimulation with T helper cells (Murphy & Weaver, 2016; Parham, 2014; Sompayrac, 2019). Once activated, B cells proliferate and go through a process of maturation. All B cells initially produce a particular type of antibody by default (IgM), but during maturation, B cells can undergo class switching to change the type of antibody secreted. They also go through a process of increasing receptor affinity, and a 'career decision' where B cells can become effector (plasma) cells or memory cells (Murphy & Weaver, 2016; Sompayrac, 2019).

There are five classes of antibody: IgA, IgD, IgE, IgG and IgM. The different types vary in terms of their shape, primary function, distribution and ability to proliferate. The primary aim of an antibody is to destroy a pathogen before it can establish a significant effect, and it can achieve this in several ways, including neutralisation, agglutination, and opinisation (Murphy & Weaver, 2016). Neutralisation refers to the process of blocking parts of the pathogen and therefore reducing the infectivity or toxicity of a virus or toxin. Agglutination refers to when antibodies cause bacteria particles to clump

together, making them attractive for phagocytosis. Opsination is a process in which a pathogen's surface is coated by the antibody so that it is more easily ingested by phagocytosis. Antibodies can also aid the immune system by activating complement, stimulating release of histamine, and sensitizing certain cells of the immune system. IgG is the most abundant type of antibody found in the blood, accounting for approximately 75% of serum antibodies. Because of this, IgG is often the focus of vaccine acquired immunity. The primary effector function of IgG is to activate the complement system. IgG is also involved in neutralisation, opsonisation and sensitizing for natural killer cells, but to a lesser extent. IgA is also important for vaccine research as it is the principle antibody class found in secretions such as saliva, and therefore easy to measure. IgA is primarily involved in transfer across the epithelium (tissue lining the organs and blood vessels), and to a lesser extent, neutralisation. It also plays a minor role in opsonisation and activating complement.

Activated B and T cells travel to the blood or lymphatic circulation or to the site of the attack to carry out their effector functions and destroy the pathogen (Sompayrac, 2019). Once the pathogens have been destroyed, the antibodies remain in the blood and short-lived effector B and T cells die, as their life span is only a few days. Memory cells are long-lived, therefore these cells remain in the body after the pathogen has been killed (Parham, 2014; Sompayrac, 2019). Memory cells can produce the correct type of antibody quickly if the same pathogen were to enter the body again in the future. These cells are essential for vaccines and immunization, and will be explored further in the next section.

1.4.2 *Vaccines and immunological memory*

Vaccines involve administering, typically by injection, a biological preparation that contains an agent able to mimic a particular pathogen. This agent may be an inactivated version of a disease, specific parts of the disease pathogen, or a live but weakened version. It is close enough to the disease that it is able to produce an immune response similar enough so that if the individual comes into contact with the specific disease at a later date, their immune system is able to draw on its past exposure with the vaccine to launch an effective attack. The mechanism that allows this to happen, and on which vaccines fundamentally rely, is called immunological memory. Immunological memory refers to the ability of the immune system to remember specific antigens that have been previously encountered and to initiate a fast and effective immune response. Vaccines aim to produce this secondary immune response, and other subsequent responses, without subjecting the body to the 'natural', potentially lethal infection, by simulating an attack without putting the body in serious danger. Because immunological memory remembers the specific diseases that come into contact with each individual over their lifetime, it will differ from person to person depending on their individual experiences with disease, therefore not everyone will have the same types of immunological memory (Sompayrac, 2019).

When an individual is vaccinated, helper T cells are activated by recognising specific vaccine antigens presented to them, and they are triggered to proliferate. Eventually, once the vaccine antigens have been destroyed, the majority of these cells die off, leaving about 10% remaining as memory T cells (Ahmed & Gray, 1996; Sompayrac, 2019). There are two types of memory T cells: central memory T cells, and effector memory T cells. Like effector T

cells, effector memory T cells can be memory CD4 or memory CD8 cells, and they remain in the tissue after an initial attack by the vaccine antigens, and can respond immediately to a secondary attack if the actual disease is encountered, when they reactivate, proliferate and destroy the invader (Parham, 2014; Sompayrac, 2019). Central memory T cells stay in the lymph nodes, and although have no effector function themselves, during a secondary attack, some of these will activate, and proliferate and differentiate into effector cells, joining those in the tissue. Some will remain and wait for another subsequent attack (Sallusto, Geginat, & Lanzavecchia, 2004; Sompayrac, 2019).

Similarly, when naïve B cells are presented with the correct vaccine antigen, they become activated and can create memory B cells. As with memory T cells, there are two types of memory B cell, long-lived plasma cells and central memory cells (Sompayrac, 2019; Yoshida et al., 2010). Long-lived plasma cells move to the bone marrow following an initial encounter with the vaccine antigens and continuously produce small amounts of antibodies that provide long lasting immunity. This means that during a secondary attack, the specific antibodies have already been produced to provide an immediate defence. Central memory B cells reside in lymph nodes, and slowly proliferate in order to replace old long-lived memory cells and maintain a constant pool of central memory B cells. They can also produce the plasma B cells involved in producing antibodies that attack the pathogen, should the pathogen reinvade.

Memory cells are more numerous and easier to activate than naïve B and T cells, thus resulting in a much quicker and more experienced attack (Parham,

2014). This secondary immune response is so effective that the infection is often cleared before symptoms can emerge (Parham, 2014). Therefore, following vaccination, if an immunised individual comes into contact with the specific pathogen mimicked by the vaccine, immunological memory will allow fast and effective protection. Immunological memory can, in some cases last a lifetime, even without experiencing a secondary attack. For instance, the childhood vaccine measles has been found to provide life-long immunity in over 96% of vaccines (Plotkin, Orenstein, & Offit, 2012). However, some vaccines such as the Tetanus and Diphtheria vaccines have been shown to last only between 10-20 years, and therefore in these cases boosters are recommended (Plotkin et al., 2012). One type of vaccine given much more frequently is the seasonal influenza vaccine. This vaccine is in fact the most commonly given vaccination in the UK (NHS Digital, 2018a). In 2018-2019 over 7.26 million people aged over 65 years old and 3.28 million people aged between 6 months and 64 years old received the vaccination (Public Health England, 2019b), representing substantial cost to the NHS. With each vaccine costing between £5.22 and £9.94 depending on the specific vaccine (British National Formulary, 2019), this constitutes a minimum spend of over £55 million each year on influenza vaccines. Given the number of people in receipt of the influenza vaccination and the high cost associated with this immunisation strategy, it would not be unreasonable to assume that the influenza vaccine is highly efficacious. However, in reality this is often not the case. The remainder of this chapter focuses specifically on influenza and the seasonal influenza vaccine. As well as describing influenza and the different types of vaccine available, this section will discuss vaccine effectiveness and explore why this appears to be sub-optimal in certain populations.

1.5 Influenza

Influenza is an infectious disease that affects both upper and lower respiratory tracts (World Health Organization, 2018b). Influenza symptoms typically include fever, cough, headache, sore throat, runny nose and muscle and joint pain. Many recover within 1-2 weeks without the need for medical intervention. However, in some populations influenza can lead to more severe illness, complications and even death. For example, influenza causes an estimated 250,000-500,000 deaths each year globally with around 8,000 annually in the UK alone (Public Health England, 2014; World Health Organization, 2018b). On an economic level, the burden of influenza on health services are substantial, with influenza-related hospital admissions estimated to cost the NHS as much as £82.9 million in 2017/2018 in more conservative estimates (National Insitute for Health and Care Excellence, 2018; NHS Digital, 2018b), with others estimating up to £125.2 million for the same season (Moss et al., 2020). The burden on primary care services is high too, with influenza-like-illness-related GP visits costing up to an estimated £27.4 million, and even more in unvaccinated patients (£168.3 million) (Pockett, Watkins, McEwan, & Meier, 2015). Estimates for the total annual burden of influenza have been made in the US, and are as high as $11.2 billion, based on 6 variables including hospitalisation, deaths and days of productivity lost (Putri, Muscatello, Stockwell, & Newall, 2018). The cost of delivering the vaccine is also high, with current coverage costing a total of over £203 million each year, of which over £122 million is spent on adults over 65 years old alone (Atkins et al., 2016).

There are four types of influenza viruses, influenza A, B, C and D. Only three of these cause illnesses in humans: influenza A and B cause seasonal

influenza epidemics, whereas influenza C usually causes only mild infections (World Health Organization, 2018b). Both influenza A and B cause similar symptoms but differ in terms of their virology. Influenza A can be broken down into several subtypes, firstly by the types of antigens found on the surface of the virus, known as haemagglutinin (H or HA) or neuraminidase (N or NA). There are 18 H and 11 N subtypes of influenza A. Any combination of these subtypes could exist, but there are two subtype combinations that routinely circulate in human populations (H1N1 and H3N2) (Centers for Disease Control and Prevention, 2021b). Influenza A can be further broken down by the different lineage and specific strain. Influenza B is not broken down into subtypes, but does also vary in terms of lineage and strain. The nomenclature used to describe a particular influenza virus takes into account these factors: first, the virus type is named (A or B), then geographic location, strain number, year of isolation and the H and N variants. For example, A/California/04/2009(H1N1) would be the nomenclature used for an American influenza A virus with the lineage number 04 from 2009.

It is possible that an individual may be a carrier of influenza but not exhibit any symptoms, and thus remain able to infect other people. For instance, it is estimated that the influenza virus is asymptomatic in approximately 75% of cases (Hayward et al., 2014; Horby, 2014). These people are able to spread the disease by infecting other people, and although the estimated level of transmission from asymptomatic influenza is varied, with estimates of between one third to one half that of symptomatic individuals, it is thought to be an important factor in the spread of influenza (Killingley & Nguyen-Van-Tam, 2013; Patrozou & Mermel, 2009).

1.5.1 *Defining influenza vaccine effectiveness*

Before discussing vaccine effectiveness and efficacy, it is important to understand how both are conceptualised and measured in the literature. Influenza vaccine efficacy refers to the degree to which a vaccine prevents influenza under ideal conditions, such as a randomised controlled trial, whereas vaccine effectiveness refers to a vaccines' performance in the real world, using observational study designs. Both are conventionally reported as percentages, calculated using one of the following formulas: (1 – odds ratio) x 100, or (1 – relative risk) x 100. When calculating vaccine efficacy, the relative risk is used and represents the relative risk of influenza-related outcomes in vaccinated compared with unvaccinated persons. In vaccine effectiveness studies, the odds ratio is used, representing the odds of vaccination between cases (i.e. those with confirmed influenza) and controls (i.e. those without influenza). Commonly, laboratory confirmed influenza is used as the main outcome in measuring influenza vaccine effectiveness and efficacy, however other outcomes such as influenza-like-illness, respiratory and/or systemic symptoms, hospital admission for influenza and/or related conditions such as pneumonia, and death may also be used.

Alternatively, vaccine effectiveness may be assessed in terms of its impact on various immunological measures of vaccine response. For instance, antibody response to vaccination is commonly used as a measure of vaccine effectiveness, in terms of either seroconversion or seroprotection (the percentage of participants meeting pre-defined thresholds denoting a degree of clinical protection), geometric mean titre (GMT) of antibody achieved post-vaccination, or the mean concentration of antibodies at post-vaccination.

Higher percentages, mean titres and concentrations represent greater clinical protection and therefore greater vaccine effectiveness.

1.5.2 *The influenza vaccine*

The influenza virus is unlike other viruses in that it requires an annual vaccination, as opposed to a one off or short series of immunizations. This is because the influenza virus goes through a process called antigenic drift, in which small genetic changes lead to different but closely related influenza viruses. These small changes eventually mean that the antibodies previously produced can no longer recognise the virus. Antigenic shift can also occur, though is less common. This process causes abrupt and major changes to viruses resulting in changes to the haemagglutinin and/or the haemagglutinin and neuraminidase combination, resulting in a new virus which again cannot be recognised by existing antibodies (Centers for Disease Control and Prevention, 2017a; European Centre for Disease Prevention and Control, 2016; Fiore, Bridges, Katz, & Cox, 2012). If an antibody in the body does not recognise the antigens on a pathogen, its receptors cannot attach and destroy or block the pathogen, allowing the influenza virus to attack and infect the body, leading to flu. Therefore, each season the most likely combinations and strains are predicted to develop the annual vaccine. This prediction is made by the WHO, and is based on year-long surveillance of influenza viruses from over 100 national influenza centres in over 100 countries. Twice a year, the WHO reviews this surveillance, as well as clinical and laboratory studies, to predict which viruses will be in circulation in the coming flu season and recommend the content of the vaccine (Centers for Disease Control and Prevention, 2018b). However, this prediction is not always accurate. For instance, some influenza virus strains may appear unexpectedly late in the

year. Given that it takes at least six months for a vaccine to be manufactured, this means that there may be insufficient time to identify, develop or prepare a vaccine. Furthermore, each year, only three to four strains are included in the annual vaccine (European Centre for Disease Prevention and Control, 2016). This means that the effectiveness of the influenza vaccine can vary greatly from flu season to flu season, depending on the specific influenza strain that is dominant during a particular season, and the success of the predictions made. For instance, Public Health England report that for the 2017-18 season overall vaccine effectiveness was 15% against laboratory confirmed influenza, much lower than previous flu seasons, which have shown an estimated effectiveness of 39.8% in the 2016/17 season and 54% in the 2015/2016 season (Public Health England, 2016, 2018a). This also means, that unlike many other vaccines, the aim of the influenza vaccine is not to eliminate or eradicate flu, but to allow better protection against that year's strain by boosting immunological responses, and therefore reducing influenza morbidity and mortality.

There are broadly two types of influenza vaccine: live attenuated vaccines and inactivated vaccines. Live attenuated vaccines contain live but weakened versions of a virus or bacteria. The weakened version is created by growing the virus in a cell type that is not its usual host, creating mutations that lead to its weakening. The nature of attenuated vaccines means that they can produce memory killer T cells, because the weakened virus is still able to infect cells and stimulate killer T cells before the body is able to destroy it. The weakened version means that it cannot cause serious disease in those with healthy immune systems and is most similar to the natural infection, which creates a strong and long-lasting immunity. However, they cannot be used in

those with weakened immune systems, as they may not be able to fight off the attenuated virus. Further, attenuated vaccines can cause a person to become infectious to other people, which can be advantageous in terms of spreading immunity, but also dangerous for those with weakened immune systems. It is also possible that a weakened virus will mutate and regain strength, before it is killed by the immune system. Currently, the live version of the influenza vaccine is only recommended in children aged over two years to less than 18 years old, and only for those who are not immunodeficient, not pregnant, and who do not have asthma (Public Health England, 2018b). This is due to safety concerns regarding use in those without strong immune systems, and an increased efficacy of the live vaccine compared to inactivated vaccines in this age group (Public Health England, 2021a). For instance, in young children, live attenuated influenza vaccines were found to be more effective compared to the inactivated vaccine, with 54.9% fewer cases of confirmed influenza in those receiving the live attenuated vaccine (Belshe et al., 2007).

Inactivated vaccines contain an inactive, or killed, version of the virus or bacteria, and are designed to not infect the vaccine recipient. Therefore, these vaccines are not dangerous for those with weakened immune systems. However, they are not as potent as live vaccines. Most influenza vaccines use an inactivated method due to the vast majority of those receiving the annual influenza vaccine being older adults, clinical at risk groups, or pregnant women (Public Health England, 2019b, 2019c), all of whom are more likely to have a weakened immune system or be at greater risk if exposed to even a mild version of flu. Inactivated vaccines have also been shown to be more effective in both healthy adults aged 18-64 years old and older adults aged 65 years and older, compared to live attenuated vaccines. For instance, a

systematic review and meta-analysis of 31 influenza vaccine effectiveness studies showed that in young healthy adults the estimated efficacy of the influenza vaccine for laboratory confirmed influenza was between 51-97% for trivalent inactivated vaccines, with a pooled estimate of 59% (Osterholm, Kelley, Sommer, & Belongia, 2012). However, the estimated efficacy in young healthy adults for live attenuated influenza vaccinations ranged from just 8-48%. For older adults, evidence suggests that inactivated vaccines are associated with a higher serum antibody response compared to the live vaccine, suggesting a more effective response to the inactivated vaccine (Powers, Sears, Murphy, Thumar, & Clements, 1989; Powers, Fries, Murphy, Thumar, & Clements, 1991).

Influenza vaccines can also vary in terms of the number of strains they protect against, the method of production, and the inclusion of an adjuvant. For example, a trivalent influenza vaccine will consist of three inactivated influenza strains, two type A strains and a type B strain, whereas a quadrivalent vaccine will contain two type A and two type B strains. Therefore, quadrivalent vaccines may offer more protection than trivalent vaccines (Centers for Disease Control and Prevention, 2018a). Most influenza vaccines are produced in eggs, but they may also be made in cells. An advantage of the cell method is that these vaccines can be given to those with allergies to eggs. Finally, some vaccines contain an adjuvant, which is an additional substance that acts to increase the effectiveness of vaccines, by accelerating, prolonging or enhancing immune responses (Sasaki & Okuda, 2000). For the 2019/2020 influenza season, for adults aged 18-64 years, two vaccines were approved in the UK by NHS England: the egg-grown quadrivalent vaccine, and the cell-based quadrivalent vaccine. In those aged 65 and over, three vaccines were

approved: the egg-grown adjuvanted trivalent vaccine, the cell-based quadrivalent vaccine, and a high dose trivalent vaccine, although this vaccine was not eligible for reimbursement and therefore not recommended (Public Health England, 2019a).

1.5.3 *Influenza and older adults*

Factors relating to the individual receiving the vaccine can also impact the effectiveness of the vaccination, including age, immune status, and pregnancy. These factors can also influence the vulnerability to influenza and related complications. For instance, older adults are disproportionately affected by pneumococcal disease (Wroe et al., 2012), yet the pneumococcal vaccine has been shown to have reduced effectiveness in this population (Kolibab et al., 2005; Schenkein, Park, & Nahm, 2008). Similarly, both the varicella-zoster virus vaccine and hepatitis B vaccines also appear to have reduced effectiveness in the older adult population, compared to younger adults (Fisman, Agrawal, & Leder, 2002; Oxman et al., 2005; Yang et al., 2016).

Older adults have also been shown to be particularly vulnerable to influenza related complications, including hospitalisations and deaths. One study using National Hospital Discharge Survey data and WHO surveillance data found that in the US, those over the age of 85 years had the highest rates of influenza-associated primary respiratory and circulatory hospitalisations at 1194.9 hospitalisations per 100 000 persons, and that this number had substantially increased in the past twenty years (Thompson et al., 2004), despite increased vaccination coverage in that time (Thompson et al., 2003).

Zhou et al. (2012) similarly found the highest influenza-related hospitalisation rates in adults aged 65 years and older, at 309 per 100 000, compared to 65.6 per 100 000 in adults aged 50-64 and 16.8 per 100 000 in those aged between 5 and 49 years. There is also evidence of a disproportionate number of influenza-associated deaths occurring in older adults, with one study suggesting that between 71-85% of deaths occurred in those aged 65 years and over (Reed et al., 2015), and further study suggesting that as many as 90% of deaths were accounted for by that age group (Thompson et al., 2003). Further, within the older adult age group, the risk of both hospitalisation and mortality appears to increase with every 10-year increase in age (Czaja et al., 2019; Sprenger, Mulder, Beyer, Van Strik, & Masurel, 1993). Systematic review evidence supports this, demonstrating higher rates of influenza-associated mortality in older versus younger adults (4-119 per 100 000 versus 0.6-8.3 per 100 000; Li et al., 2018), and all-cause mortality and hospitalisation (Mertz et al., 2013).

However, not only are those aged over 65 years at increased risk for developing influenza related complications, the balance of evidence suggests that the influenza vaccine may also be less effective in this age group compared to younger adults in terms of reducing illness. In a healthy population of people aged 18-64 years, the effectiveness of the influenza vaccine in reducing laboratory confirmed influenza has been estimated at between 50-60% (Public Health England, 2018b) or between 70-90% when the vaccine antigen is a close match to the circulating strain (Gross, 2002). In the 2016/17 season, Public Health England reported that the combined vaccine effectiveness for influenza A and B was estimated at 40.6% in 18-64 year olds, whereas no significant effectiveness was found for adults aged 65

and over (-6.3%) (Public Health England, 2018a). It should be noted however that differences between age groups are not always so large (Osterholm et al., 2012; Russell et al., 2018), particularly in seasons where there is poor matching to circulating strains (e.g., 2017/18; Public Health England, 2018d). Systematic reviews of influenza vaccine effectiveness have also documented reduced effectiveness of the influenza vaccine in protecting the elderly population from influenza and influenza-related adverse events. For instance, a systematic review and meta-analysis of 30 case-control studies estimated that influenza vaccine effectiveness for influenza symptoms, including at least one systemic and one respiratory symptom, was 51% for those aged 18-65, compared to 37% in those aged 65 and over (Rondy et al., 2017). A meta-analysis focusing on people aged 65 and older using data from ten seasons showed an efficacy of 35% in terms of reducing influenza-like illness, and 50% in terms of all-cause mortality (Vu, Farish, Jenkins, & Kelly, 2002). A second systematic review has found similar results, with an estimated effectiveness against influenza-like illness of 23% in elderly individuals, and for all-cause mortality, an efficacy of 47% (Jefferson et al., 2005). This demonstrates that the influenza vaccine effectiveness seems to be reduced in the elderly population compared to younger adults.

As well as a poorer response to vaccination in terms of illness and mortality compared to younger adults, older adults have also been shown to have poorer antibody responses to vaccination. Evidence suggests that it is the number of antibodies, rather than antibody affinity or avidity, that causes this inferior vaccine antibody response (Sasaki et al., 2011). Indeed, research investigating immune response to the influenza vaccine in older adults has primarily focused on antibody response in terms of antibody quantities. For

instance, one study found that at least 25% of healthy older adults did not develop protective antibody titres (Keren et al., 1988), and another found that only 17% generated an increase in antibody titres to all three components of a trivalent influenza vaccine, with 46% failing to respond to any at 1-month post-vaccination (Goronzy et al., 2001). In a review of 31 influenza vaccine antibody response studies, Goodwin, Viboud, and Simonsen (2006) also found reduced antibody responses to all three antigens included in trivalent influenza vaccines in older, compared to younger, adults. For all of the included antigens, older adults had a lower percentage of both seroconversion (percentage of participants with a 4-fold increase in antibodies), and seroprotection (percentage of participants with antibody titres > 40), whilst adjusting for other factors that may impact vaccine response.

Overall, while there remains some uncertainties, on balance the evidence from a range of sources seems to indicate that the influenza vaccine is less effective in older adults compared to younger adults. The question that naturally follows this observation is, why might influenza vaccines be less effective in older adults? In the final section of this chapter, the concept of immunosenescence will be introduced as a potential explanatory factor in reduced vaccine effectiveness in older adults. Immunosenescence is the term used to describe age related changes in the immune system, from which a body of research is emerging that aims to understand why this happens and that its consequences may be. This evidence will be discussed, aiming to explore why older adults seem to have this decline in immune function and vaccination response.

1.5.4 *Immunosenescence*

The immune system functions differently in older versus younger people. Older people are more susceptible to infection, neoplasia and autoimmune diseases, and show poorer response to vaccination, compared to their younger counterparts (Gardner et al., 2001; Haq & McElhaney, 2014; Pawelec, 2018). This is due to the gradual deterioration of the immune system that is part and parcel of the natural aging process. These immune changes however are not always negative; with studies showing that some aspects of the immune system are preserved and even enhanced with age (Lelic et al., 2012; Olivieri et al., 2013). Therefore, some authors argue that immunosenescence does not represent a process in which the immune system becomes non-functional or hypo-responsive, but rather represents an age-related change or 'remodelling' of the immune system (Dorrington & Bowdish, 2013).

A variety of both innate and adaptive immune processes are affected by immunosenescence, however this section will focus on those most likely to impact vaccine effectiveness. For instance, research suggests that T cells are the part of the adaptive immune system most effected by aging, and therefore likely to play a key role in the reduced effectiveness of the influenza vaccination in older adults (DeVeale, Brummel, & Seroude, 2004). Because T cells are so heavily impacted by aging, they act as an important biomarker or indicator of the development of immunosenescence. One example of the impact of aging on T cells is the shrinking, or involution, of the thymus, which begins in the first year of life and continues until death (Aspinall & Andrew, 2000; Steinmann, Klaus, & Müller-Hermelink, 1985). The thymus plays a major role in T cell maturation (Aspinall & Andrew, 2000), and this shrinking of

the thymus leads to fewer thymocytes, the precursor of T cells. This leads to a reduced number of naïve T cells, until eventually the thymus stops producing new T cells altogether. This results in a shift in the ratio of naïve to mature or memory T cells (Kudlacek, Jahandideh-Kazempour, Graninger, Willvonseder, & Pietschmann, 1995), leaving the immune system less able to fight off pathogens that have not previously been encountered.

In addition to this change to the thymus and resulting number of naïve T cells, there are also a number of age-related changes to the matured form of T cells. For example, helper T cells can become more susceptible to apoptosis with age, and may experience impaired proliferation in response to antigens as well as impaired T cell receptor sensitivity (Goronzy & Weyand, 2013; Pawelec, Sansom, Rehbein, Adibzadeh, & Beckman, 1996).

B cells are also affected by immunosenescence. As with T cells, there is also a marked decrease in the number of naïve B cells and increase in memory B cells with increased age (Ongrádi & Kövesdi, 2011). This ultimately results in reduced variance of B cells, and a reduction in antigen specific B cells. Older age has also been linked to a decreased production of antibodies in response to both initial influenza vaccination (Lelic et al., 2012) and an influenza booster (Matsushita et al., 2012). Antibodies have also been shown to have reduced potency and response diversity with increased age (Burns & Goodwin, 2001; Grubeck-Loebenstein et al., 2009). There is also a reduced production of high affinity IgG antibodies (Frasca, Riley, & Blomberg, 2005). Together, these antibody changes result in a weaker and less effective response to an attack

caused either by the vaccine antigen or secondary immune response caused by the disease pathogen.

However, several other factors may be involved in or may influence the extent of immunosenescence. For instance, nutritional status, frailty, and co-morbid conditions have all been associated with reduced immune function (Fülöp Jr et al., 1999; Gross, Quinnan, Weksler, Setia, & Douglas, 1989; Hak et al., 2002) and have direct effects on the immune system, which therefore may act as additional determinants of the immune response and thus potentially compound the effects of immunosenescence on vaccine effectiveness, Additionally, it has recently been suggested that factors such as mood, exercise and medications, rather than primary aging, may directly cause immunosenescence, and thus essentially speed up the aging process (Whaley et al., 2019).

Collectively, the immunological changes outlined above provide a likely mechanism for reduced vaccine effectiveness in older adults, and demonstrates that this may be due to a number of changes to immune function that occur with age, affecting both B and T cells. However, as will be explored in the following chapter, there are between-person differences, including potentially modifiable factors, that may influence the immune responses to vaccination within the older adult population.

1.6 Chapter summary

Influenza represents a significant public health concern and is responsible for occupying a substantial amount of NHS money and resources, as well as impacting the welfare and quality of life of a substantial number of older adults. Although vaccines are generally seen as the best way to protect oneself against an infectious disease, the influenza vaccination faces a number of challenges, including seasonal variation in the virus itself, varying types of vaccine, and immunosenescence. This phenomenon, whereby the influenza vaccination seems to be less effective in older adults, a population in the most need for greater protection, is thought to be caused by a decline in the immune system that occurs with age. This area of research demonstrates that there is a need to identify ways in which to increase vaccine effectiveness in this vulnerable group of people, a sentiment that is reflected by the Centers for Disease Control and Prevention's National Center for Immunization and Respiratory Diseases, who concluded that more effective vaccines and vaccination strategies are needed (Thompson, 2013). Therefore, the following two chapters will discuss the evidence relating to various approaches to increasing vaccine effectiveness, with a particular focus on factors that are modifiable, and specifically psychological factors.

2 Chapter 2: Psychological influences on immunity: understanding the complex nature of the psycho- immune relationship

2.1 Chapter overview

The effectiveness of vaccinations may depend on a number of different factors. The previous chapter demonstrated that one such factor is age, where despite requiring more protection than younger adults, older adults are less likely to mount robust protective antibody responses following vaccination. This chapter sets out to explore the various psychological factors also associated with immunological functioning, in order to set the scene for the following chapter, which will discuss these factors in regard to vaccine responses. Firstly, the field of psychoneuroimmunology will be described, and in doing so will provide a brief historical overview and context for the relationship between psychological factors and biological systems. This section will also describe the specific pathways through which one such psychological factor (stress) influences immune functioning, which may also extend to other psychological factors. Finally, this chapter will discuss some of the parameters that give rise to variations in how psychological factors can influence the immune system.

2.2 Psychoneuroimmunology, stress and health

2.2.1 *Psychoneuroimmunology*

Psychoneuroimmunology (PNI) refers to the study of the relationships and interactions between psychological, neural, endocrine and immune processes, and their interaction with health and disease. Some of the earliest research evidence to demonstrate a link between the body's immune system and psychological factors demonstrated that mice put under stress had increased

susceptibility to the herpes simplex virus (Rasmussen Jr, Marsh, & Brill, 1957). The field was then advanced when it was found that immune responses could be conditioned in rats (Ader, 1981; Ader & Cohen, 1975). Before these discoveries, the brain and the immune system were typically seen as distinct, autonomous systems that did not interact. However, in subsequent decades the area of PNI has gained considerable attention and there now exists an abundance of research examining these relationships. It is now understood that there exists bi-directional interactions, where the central nervous system (CNS) both receives and transmits information to and from the immune system (e.g. Besedovsky et al., 1979; Dantzer, 2004; McEwen et al., 1997). One illustrative example of this bi-directional relationship is the phenomenon of so-called 'sickness behaviours', such as increased sleep or reduced appetite, as an example. When the immune system detects the presence of a pathogen it can send signals to the brain, which will then in turn regulate behaviour in an adaptive way, resulting in the aforementioned sickness behaviours. Alternatively, both internal and external factors can cause the CNS to signal cells of the immune system to launch an immune response (Lorton et al., 2006; McCusker & Kelley, 2013), demonstrating the cross talk between the brain and immune system. This means that an immune response may be the cause of, or response to, CNS signalling. Collectively, these bi-directional interactions are vital in the maintenance of a homeostatic balance (Ziemssen & Kern, 2007).

One area that has received particular attention within the field of PNI is how various psychological factors influence immunity including the immune response to vaccinations. Although there are several factors that may influence this, stress is the most well evidenced. Therefore, the following

section will briefly consider the definition of stress, before outlining the pathways linking stress to immunity.

2.2.2 *Stress and the immune system*

The experience of stress is universal, and dates back to the beginning of organic life, in the form of predation or natural disaster (Segerstrom & Miller, 2004). Although predators no longer pose a threat, modern humans still experience stress in the form of academic exams, public speaking, relationship or work-related stressors, and financial worry, among other stressors. Although these experiences do not always require the same kind of physical response our ancestors would have experienced as the result of a predatorial encounter, such stressful stimuli nonetheless have physiological consequences. For example, sweaty palms, shaking, and increased heartbeat, are all commonly experienced in response to having to give a speech or presentation.

Despite the ubiquity of stress in modern life and common use of the term in everyday language, there still exist many different conceptualisations and definitions of stress. A discussion of these definitions goes beyond the scope of this thesis, so here we will defer to one of the most widely used and influential definitions of stress, as the appraisal of, and response to, demanding environmental situations - where the situation taxes or exceeds an individual's ability to manage it (Lazarus & Folkman, 1984). These situations are referred to as stressors. A stressor may be internal or external and has been defined as any stimulus that elicits a biological stress response (Murison, 2016), although some argue that this definition is too broad and

should only apply to events that threaten an individual's well-being (Kagan, 2016). Review evidence has shown that stress is associated with an increased risk of numerous immune related illnesses and disorders, including infectious disease, autoimmune disease, viral infection, and cancer, as well as slowed wound healing (Herbert & Cohen, 1993; Schneiderman, Ironson, & Siegel, 2005). Thus, having established what stress is, the next section of this chapter will describe the pathways that link this psychological factor to the immune system.

2.2.2.1 Stress pathways in PNI

The pathways linking stress to the immune system include both direct routes, via physiological systems, and indirect routes, via various health behaviours and practices. Researchers investigating other psychological factors, such as positive mood (affect), have proposed similar pathways (albeit with alternative names e.g. direct effects model; Pressman & Cohen, 2005). There is much overlap between the stress and positive affect models, with evidence that positive affect can impact on some of the same parameters, including both physiological markers and health behaviours (as discussed below). Whilst the stress pathways will be discussed in detail here, the models regarding positive affect will be discussed in more detail in Chapter 5.

Hypothalamic–pituitary–adrenal axis and Sympathetic-adreno-medullar axis

There are two primary pathways through which psychological stressors may have a direct impact on physiological processes, including processes related to both endocrine and immune function. Both multi-component pathways are triggered when the brain perceives a stressor, which leads to a stress

response, defined as a nonspecific response of the body to any demand for change (Selye, 1946). This stress response involves interactions between the brain and endocrine system, both of which proceed to interact with the immune system. The two key pathways thought to be involved comprise the sympathetic nervous system (SNS), including the sympathetic-adrenal-medullary (SAM) axis, and the hypothalamic-pituitary-adrenocortical axis (HPA). Both pathways are neuroendocrine systems; however, the SNS and SAM axis are comparatively faster acting, whereas the HPA axis is slower to respond (Murison, 2016).

The SNS is part of the autonomic nervous system and is involved in several physiological processes and systems, such as the cardiovascular system, respiration, and the renal and endocrine systems among others (Murison, 2016). The pathway starts in the brain, when a stressor is detected and signals are sent to the thalamus, which appraises and assigns meaning to the information. The hypothalamus is then activated, and in turn activates the autonomic nervous system (ANS), which triggers the release of noradrenaline from the adrenal glands. Simultaneously, the adrenal medulla releases adrenaline (Murison, 2016). These chemicals lead to a range of physiological and metabolic changes, the function of which is to give the body increased strength and speed (Romero & Butler, 2007). Increased blood flow allows more blood diverted from less important areas like the skin, to the muscles. The quickening of blood clotting means reduced blood loss in case of injury. Deeper breathing allows more oxygen in the lungs to supply the muscles. This response is known as the fight-or-flight response, as it allows the body to respond to the sensory information by fighting or fleeing the situation.

As well as being integral to the above fight-or-flight responses, both adrenaline and noradrenaline have also been linked to immune functioning as part of this response. Nearly all immune cells exhibit receptors for these hormones, which allows them to be targeted and regulated, particularly during times of high stress when these hormones are more abundant in the body (Ader, 2001). The effects of both adrenaline and noradrenaline on the immune system are varied. For instance, adrenaline has been associated with the redistribution of lymphocytes, a subtype of white blood cell that includes B and T cells, from storage into circulation, whilst also reducing their effectiveness (Crary, Borysenko, et al., 1983; Crary, Hauser, et al., 1983). Adrenaline can also lead to rises in cytokines such as interleukin (IL)-6, IL-8 and IL-10, as well as decreases in tumour necrosis factor (TNF)-α (Kappel, Poulsen, Galbo, & Pedersen, 1998; Van Der Poll & Lowry, 1997). Noradrenaline is associated with increased natural killer cell activity (Locke et al., 1988), and adrenaline may also be associated with increased natural killer cell numbers (Crary, Hauser, et al., 1983; Dimitrov, Lange, & Born, 2010). Conversely, other research has found that these hormones are associated with decreased production of and response to cytokines (Amason, 1991). Thus, the effects of adrenaline and noradrenaline seem to be diverse, with some immunosuppressive effects and some consistent with upregulation.

A second pathway involved in the stress response is the HPA axis. Compared to the SAM system pathway, it is slower and not as easily activated (Murison, 2016). Activation of the HPA axis begins when the hypothalamus synthesizes and secretes corticotropin-releasing factor, which regulates the pituitary gland (Padgett & Glaser, 2003). The pituitary gland then stimulates the release of adrenocorticotropic hormone into the blood stream. Adrenocorticotropic

hormone then travels to the adrenal cortex, which then produces glucocorticoid hormones such as cortisol (Stowell, Robles, & Kane, 2012). The production of cortisol also leads to a number of biological and physiological changes (Romero & Butler, 2007). These changes include an increase in access to energy stores, as well as increased fats and protein mobilisation to supply energy to the muscles. There are also increases in pain threshold in case of injury, and inhibition of certain immune functions such as inflammation.

Cortisol also influences the functioning of the immune system, through the same mechanism as adrenaline and noradrenaline – receptors on the surface of the immune cells. The effects of cortisol on these immune cells are similarly broad, however early work suggested that they were predominantly immunosuppressive. Glucocorticoids are associated with reductions of lymphocytes, including T cells and monocytes, macrophages, and leukocytes (Ashwell, Lu, & Vacchio, 2000; Black, 1994; Fauci & Dale, 1975), as well suppressed natural killer cell activity (Eddy, Krukowski, Janusek, & Mathews, 2014; Gatti et al., 1987; Mavoungou, Bouyou-Akotet, & Kremsner, 2005). High levels of glucocorticoids can also lead to increases in the synthesis of anti-inflammatory proteins, as well as reductions in pro-inflammatory cytokines and chemokines (Barnes, 2001; Joyce, Gimblett, & Steer, 2001; Kunz-Ebrecht, Mohamed-Ali, Feldman, Kirschbaum, & Steptoe, 2003; Mawdsley & Rampton, 2005; O'connor, O'halloran, & Shanahan, 2000; Ray & Sehgal, 1992). As a consequence of lower levels of cytokines, circulating lymphocytes may also be less responsive, as they are less able to receive signals from the cytokines (Sapolsky 2004). However, glucocorticoids also result in a redistribution of immune cells, thus lower levels in certain blood lymphocytes may not

constitute immunosuppression, but migration to areas where antigens are more likely to be encountered (Dhabhar & Mcewen, 1997; McEwen et al., 1997). Indeed, more recently it has been argued that cortisol may be both immunosuppressive and immune enhancing, depending on the context (Cain & Cidlowski, 2017). For instance, at low levels, cortisol has been linked to increases in the production of proinflammatory cytokines, useful for promoting cell mediated immunity (Mawdsley & Rampton, 2005; Renz et al., 1992). On the other hand, others have found that low levels of cortisol can be equally harmful as higher levels, as this may result in uncontrolled inflammatory diseases (Sternberg, 2006). Together, this demonstrates the complexity of immune function changes as a result of cortisol release, and suggests that rather than global immunosuppression, immune dysregulation may be a more accurate description of these processes.

The activation of these pathways allows the body to respond to a stressor. Once a stressor has been dealt with, the bodily systems including immune functioning, seek to return to function as normal, thus maintaining homeostasis. Whereas the SNS triggers the SAM stress response, it is the parasympathetic nervous system (PNS) that helps to switch off this response once the hypothalamus perceives that the situation is over. Similarly, the HPA axis is switched off when cortisol levels are detected as being too high, causing the hypothalamus and hippocampus to shut down this pathway through a negative feedback mechanism (McEwen, 2002; Vermetten & Bremner, 2002). This process of maintaining homeostasis is referred to as allostasis; the adaptation of the body to acute stressors by means of the stress response (McEwen 1998; Sterling & Eyer 1988). In the short term, this allostatic process is adaptive and essential to survival. However, it is thought

that long term activation of these pathways may lead to physiological health problems (McEwen, 1998, 2019). For instance, allostatic load and overload refers to the wear and tear on the body that can be caused as a result of a failure to maintain allostasis due to, for instance, repeated exposure to multiple novel stressors or delayed shut down of the stress response (McEwen, 2017; McEwen & Stellar, 1993). This can lead to interruptions in normally effective bodily systems including the immune system, resulting in increased risk of illness. Thus, in certain situations, the normally adaptive stress pathways described here can become maladaptive and potentially harmful.

Behavioural pathways

In parallel to the direct effects of psychological stress on the body via the stress pathways described, the experience of stress may also indirectly impact immune functioning. Stress can lead to an alteration in behaviour in a way that leads to an increased risk of compromised or suppressed immune function (Kiecolt-Glaser & Glaser, 1988). Poor sleep, decreased exercise, and smoking are all behaviours that may increase during times of stress, but may also negatively impact our health and immune function (Åkerstedt, 2006; Cohen & Lichtenstein, 1990; Stetson, Rahn, Dubbert, Wilner, & Mercury, 1997). For instance, a study of 180 students showed that compared to non-stressed participants, those about to undergo academic examinations showed increases in smoking and alcohol consumption, as well as decreases in physical activity (Steptoe, Wardle, Pollard, Canaan, & Davies, 1996). In turn, smoking has been associated with a host of adverse immune changes, including increased white blood cell counts (Arcavi & Benowitz, 2004), which is an indicator of systemic inflammation associated with mortality (Margolis et

al., 2005; Shankar et al., 2006) and reduced production of antibodies necessary for fighting viruses and bacteria (Arcavi & Benowitz, 2004). Smoking is also associated with a reduced quantity and function of natural killer cells, potentially resulting in an increased risk of infection and cancer (Mehta, Nazzal, & Sadikot, 2008). Thus, this clearly shows how, as well as directly effecting immune functioning through the above described physiological pathways, stress can also indirectly impact immune functioning through behaviours associated with times of increased stress.

2.3 Variations in the psycho-immunological relationship

While the above has illustrated some of the pathways by which stress, and by extension other psychological factors, can impact on the immune system, it is overly simplistic to consider such responses as uniform across people. Not everyone will react to a stressor in the same way, and not all types of stressors have equal effects on immune functioning. Equally, different features of other psychological factors such as positive and negative affect may also influence how the immune system functions.

Whilst one approach to investigating the variations in the psycho-immune relationship is the study of individual differences, which have been explored in the transactional theory of stress and coping (Lazarus, 1966; Lazarus & Folkman, 1984), this section will explore features of stressors, positive, and negative affect that have been shown to influence the nature of the immune effects. Specifically, in the context of stressors, the effect of duration will be explored, and in the context of positive and negative affect, the focus will be on affect valence, arousal, and state as compared to trait affect.

2.3.1 ***Stressors***

Early models of stress suggested that the effects of the stress response are broadly immunosuppressive (e.g. Selye 1975). Although there is plenty of evidence to support this theory, Segerstrom and Miller (2004) point out that it is not evolutionarily adaptive for all immune function to be supressed in response to a physical or psychological stressor. More recent models of stress have proposed a distinction between acute and chronic stressors, which have differential effects on the immune system (Dhabhar, 2001; Dhabhar & Mcewen, 1997; Dopp, Miller, Myers, & Fahey, 2000; Segerstrom & Miller, 2004). According to these models, acute stressors typically result in enhanced immune functioning, specifically enhanced natural immunity, which allows for fast and effective responses to potential invaders, whereas chronic stressors lead to global immunosuppression. Some of the evidence supporting the impact of stressor duration is considered below.

2.3.1.1 Acute stressors

Acute stressors refer to stressors that are time limited, and are often associated with an element of unpredictability, threat to ego, or novelty. Acute stressors may take several forms, including experimental stressors such as the Stroop test, speech tasks, or mental arithmetic, and naturalistic stressors such as exams, medical tests and results, or natural disasters. It is useful to examine both types of acute stressor, as each approach has its own strengths and weaknesses. Experimental stressors allow for many potentially confounding variables, such as intensity and duration, to be controlled for, however often lack real-world applicability. Conversely, whilst natural

stressors are often highly applicable, they are more difficult to control for such confounders.

There is a vast literature investigating the effects of both acute experimental and naturalistic stressors on immune functioning. Experimental acute stressors have been associated with increases in both innate immunity parameters, including absolute numbers of natural killer cell and natural killer cell activity (Van Der Pompe, Antoni, Visser, & Heijnen, 1998), as well as adaptive immune parameters, including total IgA antibody levels (Ring et al., 2000; Takatsuji et al., 2008; Willemsen et al., 1998). Together these studies suggest that acute stress may be related to enhanced immune function. Indeed, in their meta-analysis including 98 studies of acute experimental stressors, Segerstrom and Miller (2004) reached a similar conclusion, with significant and reliable increases in various immune parameters, particularly those related to natural immunity. This is consistent with the models of stress outlined in section 2.2.2, with a shift towards natural immunity, and away from specific immunity. Naturalistic stressors, on the other hand, were associated with a pattern of suppression of cellular immunity along with a shift towards humoral immunity (Segerstrom & Miller, 2004). This is echoed in more recent studies demonstrating enhancement of humoral parameters, such as IgA response, and either no effect or suppression of parameters relating to cellular immunity, such as natural killer cell counts (Assaf, Al-Abbassi, & Al-Binni, 2017; Marshall Jr et al., 1998; Maydych et al., 2017; Murphy, Denis, Ward, & Tartar, 2010; Witek-Janusek, Gabram, & Mathews, 2007). Thus, this suggests that acute stressors may be associated with both immune system enhancement and suppression, depending on the specific parameter and stressor in question. It is worth considering, however, that other differences

between experimental and naturalistic acute stressors may account for this apparent differential immune effect. For instance, experimental stressors such as speech or mental arithmetic tasks are likely to be short-lived, limited to a single experimental session. On the other hand, naturalistic stressors such as exam periods are likely to be longer, albeit not chronic. For instance, they may encompass the days or weeks leading up to the exam, as well as the exam itself. Thus, the duration of 'acute' may vary between stressor types, potentially resulting in differing immune effects.

2.3.1.2 Chronic stressors

One type of stressor that has repeatedly been identified as having some of the most persistent negative effects on immune function are those that last over a long period, i.e. chronic stressors. In contrast to acute stressors, chronic stressors are stable and enduring, meaning that often an individual does not know when it will end, if at all. This type of stressor has been widely studied, with meta-analytic and narrative reviews showing associations between chronic stress and various negative immune and health outcomes (Herbert & Cohen, 1993; Lovell & Wetherell, 2011; Segerstrom & Miller, 2004; Vitaliano, Zhang, & Scanlan, 2003; Whittaker & Gallagher, 2019).

One of the most commonly studied types of chronic stressor is caregiving, which not only represents a demanding and stable stressor, but also often falls to family or spouses, who themselves may be elderly or ill-prepared (Majerovitz, 2007; Pariante et al., 1997). The negative effects of caregiving are particularly salient for the elderly, who are not only more likely to spend more time caregiving (Gallagher, Phillips, Evans, et al., 2008), but are also

more likely to experience significantly poorer immune functioning compared to both younger caregivers and age matched non-caregivers, as assessed by a variety of immune parameters. Indeed, caregivers have been found to have decreased natural killer cell activity response to cytokines (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994), lower percentages of T cells (Pariante et al., 1997), lower sIgA secretion rates (Gallagher, Phillips, Ferraro, Drayson, & Carroll, 2008), and decreased mitogen-induced lymphocyte proliferation, an indication of poorer immune functioning, compared to age-matched non-caregiving controls (Bauer et al., 2000).

Other forms of chronic stress, including divorce, mothering preterm infants, bereavement, and homelessness have also been associated with various immune function impairments, including parameters relating to both natural (innate) and specific (adaptive) immunity, as well as both cell mediated (i.e., primarily mediated by T cells) and humoral immunity (i.e., antibody-mediated) (Arranz, de Vicente, Muñoz, & De la Fuente, 2009; Bartrop, Lazarus, Luckhurst, Kiloh, & Penny, 1977; Gennaro et al., 1997; Kiecolt-Giaser et al., 1993; Kiecolt-Glaser et al., 1987; Kiecolt-Glaser, Glaser, & Christian, 2014; Kiecolt-Glaser et al., 1988). Therefore, taken together, the evidence suggests that chronic stressors are associated with widespread negative immune changes. This is in contrast to acute stressors, which show some beneficial effects on immune function, depending on the specific type of acute stressor. Thus, the duration of a stressor, and by extension, other psychological factors, can certainly give rise to variations in the immune response.

2.3.2 *Affect*

There is substantial evidence that emotions, or affect, can influence physical health (Cohen & Pressman, 2006; Cuijpers & Smit, 2002; Pressman, Jenkins, & Moskowitz, 2018). Affect is typically split into two broad constructs: positive affect (PA) and negative affect (NA). Historically, the effects of NA and related emotions - such as anger, anxiety, and depression - have received greater research attention, but increasingly the influence of PA on health is being recognised (Cohen & Pressman, 2006). PA refers to feelings that reflect a level of pleasurable engagement with the environment (Clark, Watson, & Leeka, 1989), whereas NA is less clearly defined, but may refer to a more general feeling of unpleasurable and aversive mood states (Lazarus & Folkman, 1984; Watson, Clark, & Tellegen, 1988). Although NA may be viewed as at the opposite end of the same construct as PA, some argue that positive and negative affect are in fact distinct and independent of each other (Pressman & Cohen, 2005). Stress is also closely linked to NA, although the two are conceptually different. Unlike NA, stress is often defined as the appraisal of and response to demanding environmental situations (as previously outlined in section 2.2.2). There is often considerable overlap between the two when discussed in the literature, and they are widely considered as highly correlated constructs that are often highly conflated (Du, Huang, An, & Xu, 2018; Lee, Sohn, Lee, Park, & Park, 2005). Indeed, much of the stress literature likely applies to NA to an extent, however, in the context of this thesis they will be considered independently, and discussion of NA studies will be limited to those that explicitly discuss NA, rather than related constructs such as stress.

As well as valence (i.e. positive and negative affect), affect may also vary in terms of both its level of activation, or arousal, and by its duration, in that it may be state or trait. Each of these parameters may influence the impact of affect on specific immune responses. Thus, the remainder of this section discusses the impact of both high versus low arousal affect, and state compared to trait affect, in terms of their differential effects on immune function, and in respect to both positive and negative affect.

2.3.2.1 Valence

Mood induction studies, where methods such as films, hypnosis, or music are used to induce specific moods, are often used to investigate the effects of mood on the immune system. The majority of these studies show benefits of positive mood induction on a variety of immune parameters including antibodies (Berk, Felten, Tan, Bittman, & Westengard, 2001; Dillon, Minchoff, & Baker, 1986; Labott, Ahleman, Wolever, & Martin, 1990; Lambert & Lambert, 1995; Perera, Sabin, Nelson, & Lowe, 1998), white blood cell counts (Berk et al., 2001; Futterman, Kemeny, Shapiro, & Fahey, 1994; Futterman, Kemeny, Shapiro, Polonsky, & Fahey, 1992) and cytokines (Mittwoch-Jaffe, Shalit, Srendi, & Yehuda, 1995; Ryff, Singer, & Dienberg Love, 2004). On the other hand, negative mood induction is more commonly associated with immunosuppressive effects, such as reduced sIgA levels, reduced cytokines, and increased inflammatory cytokines (Labott et al., 1990; Mittwoch-Jaffe et al., 1995). However, there is evidence that negative mood induction can have some positive effects, with some studies finding no significant differences positive or negative mood induction groups, in terms of sIgA levels and PHA stimulated proliferation (Futterman et al., 1992; Hucklebridge et al., 2000; Knapp et al., 1992; Njus, Nitschke, & Bryant, 1996). Thus, whilst in general

valence seems to cause variation in the relationship between psychological factors and immune response, this has led some to question whether it is in fact the level of activation that may be more important in terms of immune response, with high activation PA *and* NA being potentially more beneficial than low activation affects.

2.3.2.2 High versus low arousal

One conceptualisation of affect describes a circumplex model with two dimensions, including activation (aroused versus unaroused), as well as valence (Russell, 1980). In this model, high activation refers to states such as excitement, and low activation refers to states such sadness or calm. Many researchers have theorised that high affective activation is equivalent to physiological arousal and it is through these pathways that affect may influence health (Cohen, Kessler, & Gordon, 1997; Krantz, Glass, Contrada, & Miller, 1981). Therefore, much of this research focuses on high activation dimensions of PA, rather than low activation dimensions such as 'calm' (Marsland, Pressman, & Cohen, 2007). The remainder of this section will focus on studies including measures of both high and low activation affective states.

Results from the limited number of studies including these measures, however, are not straightforward. For instance, whilst high arousal NA states such as 'angry', have been associated with better immune functioning when compared to low arousal 'depressed', 'happy-relaxed', another low arousal state, resulted in better functioning compared to both NA states (Zachariae et al., 1991). Similarly, Futterman et al. (1994) found that PA was associated

with increased immune response compared to NA states, with no difference between high and low activation states. Finally, McCraty, Atkinson, Rein, and Watkins (1996) found that music designed to facilitate a balance of 'calm yet energetic alertness' led to a significant increase in sIgA concentrations. Together, this limited evidence suggests that the beneficial effects of PA on the immune system may be independent of activation level, whereas the beneficial effects of NA may only exist for high activation negative moods such as anger. Alternatively, it may be that a balance between high and low arousal is most important in determining effects on the immune system.

However, these inferences are restricted by several limitations of the literature. For instance, these studies often lack well-matched control groups, which, coupled with a high degree of variation in the specific immune parameters assessed between studies, makes direct comparisons impossible. Additionally, of the three studies discussed above, two assessed a variety of different immune parameters, increasing the likelihood of a type one error, finding a significant effect for at least one of the parameters by chance. Finally, all three studies also had small sample sizes (n=94, 16 and 10, respectively), yet failed to report details of a power calculation. Therefore, the studies are likely to be underpowered, further increasing the chance that any significant effects seen are unlikely to reflect the true effect. Thus, this evidence should be interpreted with caution.

2.3.2.3 State versus trait affect

State affect refers to relatively short-term transient emotions, whereas trait refers to more stable, disposition-like affect (Pressman & Cohen, 2005). Whilst

trait affect may be more helpful when measuring distant outcomes such as mortality, state affect is most relevant for brief studies of short-term physiological function, including immune functions (Pressman, Jenkins, & Moskowitz, 2019).

Despite being arguably more appropriate for short-term immune function measures, compared to trait affect, state affect is relatively under-studied. Further, the limited studies that have assessed state affect have yielded conflicting results. On the one hand, some studies have demonstrated that daily mood assessments are associated with antibody response to a novel antigen, where antigen specific sIgA was higher on days with higher positive mood ratings, whereas days with high negative mood were associated with lower sIgA levels (Stone, Cox, Valdimarsdottir, Jandorf, & Neale, 1987; Stone et al., 1994). However, in complete contradiction to these studies, Evans, Bristow, Hucklebridge, Clow, and Walters (1993) found that increases in non-specific sIgA concentration and secretion rate were associated with negative mood, whereas positive mood was not associated with sIgA at all. Together these studies suggest that perhaps both positive and negative state affect are associated with changes in sIgA. However, these inconsistencies may also be explained by factors such the timing of sIgA measurement, differences in the marker of immune activity measured, or a lack of statistical power given the small sample size in Evans et al.'s study (n=12). Evidence from the previously described mood induction studies also speak to the impact of state affect on immune parameters, be it positive or negative affect, including changes to sIgA amongst others (see section 2.3.2.1).

The evidence for trait affect is also somewhat conflicting. For instance, higher levels of trait PA have been associated with higher numbers of natural killer cells and natural killer cell cytotoxicity, whereas trait NA was found to be associated with lower natural killer cell cytotoxicity (Valdimarsdottir & Bovbjerg, 1997). Similarly, trait PA, when assessed in terms of 'vigour', has been associated with greater natural killer cell activity and lower antibody responses to a latent virus, indicative of effective immunity (Lutgendorf et al., 2001). When assessed in terms of being 'content', higher levels of trait PA have also been associated with higher numbers of natural killer cells and cytotoxic T cells in the week before a cold sore outbreak. Those with low trait happiness and hopefulness, on the other hand, showed lower CD8+ cell levels compared to those high in happiness (Logan, Lutgendorf, Hartwig, Lilly, & Berberich, 1998). However, in contrast, Moss, Moss, and Peterson (1989) found no effect of trait mood on natural killer cell cytotoxicity.

Thus, the evidence suggests that the relationship between affect and the immune system may be influenced by the nature of the affective mood, be it state or trait. The evidence for trait affect is more plentiful and consistent, suggesting beneficial effects on the immune system associated with trait PA and negative effects associated with trait NA, whilst evidence for state affect is equivocal. However, these findings should be interpreted in the context of their limitations, including problematic variation in the definition and measurements of both 'state' and 'trait' affect. For instance, the definitions of trait affect in the studies cited included mood that day (e.g., Valdimarsdottir & Bovbjerg, 1997), 7 days (e.g., Lutgendorf et al., 2001), or daily mood averaged over a week (e.g., Logen et al., 1998), not only introducing variation but also questions regarding whether they truly represent trait, rather than

state affect (Pressman & Cohen, 2005). The specific measure of mood also varied, with some employing measures that include adjectives such as 'vigour' which arguably may represent underlying health status, rather than purely PA. Overreliance on retrospective self-report measures is also problematic, with research showing that memory for past events and psychological states can be unreliable (Giske, Sandvik, & Røe, 2010; Miron-Shatz, Stone, & Kahneman, 2009; Shiffman et al., 1997), and may be influenced by other factors including cognitive heuristics - shortcuts based on expectations (Brown & Astell, 2012; Smyth & Stone, 2003; Stull, Leidy, Parasuraman, & Chassany, 2009). This may particularly be the case in older adults, who not only show unreliable memory, but also demonstrate increased confidence in their memory, compared to younger adults (Dodson & Krueger, 2006).

Overall, this evidence demonstrates that the nature of affect is highly complex in terms of its impact on immunological functioning, and again highlights that variations in specific parameters, in the context of psychological experiences, can cause variations in the specific effects they have on immune function.

2.4 Chapter summary

The first section of this chapter set out to provide background and context to the field of PNI and demonstrate the evidence for relationships and pathways between neurological, endocrine and immunological systems. It is clear from the evidence that there are links between the experience of stress (and by extension other psychological factors), the body's physiological systems, including both endocrine and immune systems, and clinically relevant health outcomes. However, these relationships are complicated. Indeed, as

discussed in section 2.3, context has been shown to be highly important when considering the complexities of various psychological factors on the immune system, and on subsequent illness.

Overall, the evidence discussed up to this point clearly demonstrates how environmental and psychological experiences, can have consequences for the body's physiological systems, potentially leading to dysregulation, resulting in illness and infection. It has also demonstrated that, using these pathways, it is possible to intervene to improve immune functioning, and potentially health outcomes. Therefore, having demonstrated that the immune system can be influenced by various psychological factors, the next chapter focuses on these factors in relation to vaccine effectiveness, with the goal of identifying factors for intervention.

3 Chapter 3: Psychological influences on immunity: implications for vaccines

3.1 Chapter overview

The previous chapter demonstrated the potential pathways through which psychological factors can influence immune function. It also demonstrated the complex nature of this psycho-immune relationship, highlighting that several parameters can influence the specific consequences on immune function and determine their clinical relevance across diverse outcomes, including wound healing, responses to viral pathogens, and also vaccination effectiveness (Cohen, Doyle, Turner, Alper, & Skoner, 2003; Pedersen, Zachariae, & Bovbjerg, 2010; Song et al., 2020; Walburn, Vedhara, Hankins, Rixon, & Weinman, 2009).

Thus, this chapter aims to examine the evidence that psychological factors influence vaccine responses specifically, exploring the clinical relevance of such factors and how they may be operationalised in order to improve vaccine effectiveness. This discussion of evidence, where possible, will focus specifically on influenza vaccine response in the older adult population. Firstly, the distinction between modifiable and non-modifiable factors that influence vaccination outcomes will be made, before discussing the evidence for three of the most prominent modifiable psychological factors: stress, positive, and negative affect. Finally, this chapter will aim to identify the psychological factors that may be considered for intervention to improve influenza vaccine effectiveness in older adults.

3.2 Modifiable and non-modifiable influences on vaccination effectiveness

Many factors can impact the effectiveness of vaccinations. As Chapter 1 described, age is associated with influenza vaccine effectiveness, as well as factors such as genetics and past exposure. However, as these factors cannot be changed, they offer little opportunity to improve vaccine effectiveness. In contrast, other factors linked to vaccine responses are potentially modifiable, and therefore may be important areas for research in terms of improving and enhancing vaccine effectiveness.

Modifiable factors include pharmacological, psychological and behavioural factors, and may be related to the vaccine itself, the procedures involved in administering the vaccine, or to the individual receiving the vaccination. For example, vaccine effectiveness may be influenced by the type of vaccine, use of adjuvants (substances which enhance the body's immune response to an antigen), or dosage (Domnich et al., 2017). However, the development of novel vaccines and vaccine adjuvants is a lengthy and expensive process (Andre, 2002; Gouglas et al., 2018; World Health Organization, 2013). Further, as evidenced in Chapter 1 of this thesis, despite many decades of research the protection gap between older adults and younger adults remains substantial. Patient-related factors, on the other hand, may provide a comparatively less costly and more rapid approach to enhancing vaccine effectiveness. In terms of patient-related factors, nutrition, sleep, exercise, stress, and mood have all been associated with vaccine efficacy (Calder, 2013; Irwin, 2015; Marsland et al., 2007; Pascoe, Singh, & Edwards, 2014; Pedersen, Zachariae, & Bovbjerg, 2009). The following section will therefore focus on modifiable patient-related influences on vaccine efficacy,

with particular focus on psychological factors, including stress, positive, and negative affect. It should be noted that there is a large body of literature focusing on behavioural influences on immune response, and vaccine response specifically, however as this is not the focus of the current thesis, this literature will not be covered in detail. The following sections will then discuss the evidence pertaining to which of these factors may be the best, or most influential, target for interventions, and a subsequent programme of work in which this thesis is situated.

3.3 Psychological factors and vaccines

The remainder of this section will discuss various psychological factors that may be related to vaccine response. Where possible, the discussion will be limited to evidence in older adults, as this population is most in need of effective vaccines. Where there is no evidence available for the older adult population, evidence from other populations and how this evidence might translate to the older adult population, will be considered. Further, evidence of the influenza vaccination will be prioritised where available, but where such data are sparse other vaccination types will be discussed.

3.3.1 *Stress*

Section 2.2.2.1 demonstrated the existence of pathways linking the experience and appraisal of stress and the immune system. A large body of evidence has also accumulated linking psychological stress to influenza vaccine response. In a systematic review, Pedersen et al. (2009) concluded there was strong evidence of a negative association between naturalistic stressors and peak antibody titres, in both young and older adult populations, though with a stronger association in the older adult population. Similarly, in a

narrative review, Cohen, Miller, and Rabin (2001) concluded that the evidence supports a relationship between stress and antibody responses to immunisation, which again was most prominent in older adults. However, the nature of this association depended on the type of stress (chronic or acute). Thus, this section will consider this evidence in regards to both acute and chronic stress separately, in the older adult population where evidence is available.

Chronic stress

As outlined previously, caregivers are often studied in relation to chronic stress due their natural exposure to and long-term stressful environments. Indeed, caregiver burden and burnout are well documented in older adults (Adelman, Tmanova, Delgado, Dion, & Lachs, 2014; Bastawrous, 2013; Hiyoshi-Taniguchi, Becker, & Kinoshita, 2018). Compared to matched controls, elderly caregivers also have poorer antibody response to influenza vaccination, with one study demonstrating that this group are significantly less likely to show a 4-fold increase in antibody titres at 4 weeks post-vaccination (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996). Caregivers were also significantly less likely than non-caregivers to show a good response to the vaccine (38% versus 66%), with those over 70 years old even less likely (26%). This effect also extends to former caregivers. In a subsequent study spanning two flu seasons, Glaser, Kiecolt-Glaser, Malarkey, and Sheridan (1998) found that both current and former caregivers had significantly lower antibody titres to the influenza vaccine than controls. This was true despite caregiver groups being more likely than controls to have had the previous years' vaccinations. These findings suggest that once caregiving responsibilities have ended, vaccine responses do not improve to match those

observed in non-caregiving controls, as might be expected. It is unclear whether this reduced antibody response is due to a lasting effect of caregiver stress, or as a result of ongoing effects of bereavement. However, both studies described here do have several methodological limitations. Both had small sample sizes (N=64 and 124, respectively), and controls were recruited from adverts, which may have resulted in a selection bias. Both studies also did not report antibody response to specific antigen strains, meaning that this aspect of vaccine response cannot be assessed. Finally, both studies failed to include a formal measure of stress. Whilst it is likely that caregivers are more stressed than controls, this was not confirmed in the current studies and so cannot be confidently inferred. Instead, it would only be correct to ascertain that caregiving is associated with poorer antibody response to vaccination. However, studies that do include both a measure of stress and results for each vaccine strain confirm the relationships between caregiving, stress, and vaccine response, demonstrating that not only are elderly caregivers significantly more stressed, they also demonstrate significantly poorer antibody responses to at least one of the influenza vaccine strains compared to control participants (Vedhara et al., 1999).

However, all of the studies discussed here are limited by the issue common to all observational evidence, which is the potential of confounding factors, meaning that cause and effect cannot be established. Some of these factors are addressed to a degree. For instance, all studies have included measures of potential confounding variables, such as health behaviours including alcohol consumption, sleep, exercise and nutrition, as well as health conditions and depression. However, when differences were found between groups, these were not always accounted for in the main statistical analysis.

Therefore, it is possible that the relationship between stress and vaccine response may be influenced by these other factors.

To further examine the association between chronic stress and influenza vaccination response in older adults, some studies have employed stress reduction interventions, to assess whether this leads to enhanced immune responses, as would be predicted based on the observational evidence. However, this evidence is inconsistent. On the one hand, elderly carers randomised to an 8-week stress management intervention were significantly more likely to generate an immune antibody response indicative of clinical protection to the influenza vaccine compared to control participants (50% vs 7%; Vedhara et al., 2003). On the other hand, Hayney et al. (2014) found no differences between 6-weeks of a mindfulness-based stress reduction (MBSR) intervention and a control condition in terms of influenza vaccine response, although they did find associations between those achieving seroprotection and lower levels of perceived stress. Further, incidence, duration, and severity of acute respiratory illness episodes were found to be 33-35% lower in the MBSR group compared to the control group. It is possible that the lack of association between stress reduction and vaccine response may be due to a particularly effective vaccine, leading to possible ceiling effects. Alternatively, it may be due to the specific immune parameters that were measured. Indeed, as previously discussed, McElhaney et al. (2006) demonstrated that in older adults, cell-mediated immune parameters were better predictors of laboratory-confirmed influenza than antibody levels. Nevertheless, many studies have found antibody levels to be sufficient as a marker of seroprotection (e.g., Talbot et al., 2015; Vedhara et al., 2003).

Populations other than older adults have also seen benefits of stress reduction in terms of vaccine responses. In a study of 41 healthy working age adults receiving the influenza vaccine, Davidson et al. (2003) compared an 8-week mindfulness meditation training programme to a wait-list control group. Following the intervention, those in the meditation group had a significant reduction in anxiety, as well as significant increases in antibody titres to the vaccine, compared to control participants. Given the age of participants, and the fact that the mindfulness intervention took place during working hours, at a place of work, the application of these results to older adults may be limited. However, the authors assert that a non-work environment may be more conducive to the intervention, thus the benefit for older adults, who are not likely to take part in a work-based intervention, may be even greater.

Acute stress

There are currently no observational studies investigating acute stress and influenza vaccine response in older adults. However, the impact of acute stress has been studied extensively in other populations and vaccinations, which suggest a negative effect on vaccine response. This is certainly evident in a study of 48 medical students receiving a series of hepatitis B inoculations during academic examinations (Glaser et al., 1992). Those who were less stressed were more likely to seroconvert (develop hepatitis B specific antibodies) after the first injection, indicating that acute stress was associated with poorer vaccination responses. Similar results were observed for a novel antigen, keyhole limpet hemocyanin, in 45 students either at the time of viva voce examination, or during an examination free time (Smith et al., 2004). Results from delayed hypersensitivity skin tests, an assessment of cellular immunity, showed that students undergoing examinations were less likely to

develop delayed hypersensitivity responses to the vaccine, indicating poorer immune function, although other immune parameters such as T cell proliferation and antibody production were not affected. However, the applicability of these findings to the specific situation of interest in this thesis is severely limited, not only by the population, who would expect different responses to that seen in older adults, but also by the antigen itself. Given the lack of antibody response, it could be theorised that this novel antigen may not lend itself well to comparison with antigens found in influenza vaccinations, thus limiting the ability to apply these results to influenza vaccine responses.

There are also no interventional studies investigating acute stress and vaccine response in older adults. However, evidence from younger adults and students undergoing acute stress induction suggests that acute stress may enhance immune function, rather than suppress, as seen in chronically stressed individuals. This has been demonstrated in a study comparing acute physical stress, acute mental stress, and a control condition in healthy young adults, prior to receiving the influenza vaccination (Edwards et al., 2006). Results showed that women in the control condition exhibited poorer antibody responses to one of the strains (H3N2) at four-weeks post-vaccination, compared to those in the two acute stress conditions. In a study using similar methodology, antibody responses to the meningococcal A vaccination were found to be enhanced in the exercise and mental stress groups compared to the control condition for male participants (Edwards et al., 2008). Both studies suggest that acute mental and physical stress may enhance vaccine response in young adults. It should be noted that in both studies, the active interventions took place in groups whereas the control conditions did not. This

may have introduced a number of factors, both positive (e.g. social interaction) and negative (e.g. competition, social comparison, distraction), which may have influenced the effects of the interventions on vaccine response.

Whilst the previous studies investigated the effect of acute stress induction, the relationship between this form of stress and vaccine response may also be examined using acute stress reduction interventions. In such a study, 70 students were randomly assigned to receive weekly 45-minute massage before a period of examination, or to a control condition, before receiving the hepatitis B vaccination (Loft et al., 2012). Following the intervention, both groups experienced increases in perceived stress and anxiety in response to examinations, suggesting that massage was not effective in negating the stress of examination. Further, the massage intervention did not lead to an increase in vaccination antibody response. In fact, those in the massage condition had significantly lower antibody levels than control participants at both post vaccination time points. Given that massage was unable to reduce stress, inferences regarding the impact of acute stress reduction on vaccine response are limited. However, given that the evidence discussed here suggests that acute stress may have beneficial effects on vaccine responses, it is worth considering that it may not be appropriate to try to reduce this form of stress with the aim of improving vaccination response. Conversely, evidence suggests that massage not only reduces chronic stress (Cady & Jones, 1997; Davis, Cooke, Holzhauser, Jones, & Finucane, 2005; Shulman & Jones, 1996), but may also have beneficial effects on various aspects of immunity (Hernandez-Reif et al., 2004; Ironson et al., 1996; Lovas et al., 2002), suggesting that the effect of stress reduction on antibody levels may depend on the nature of the stressor.

Life events

Life events, even seemingly positive events, are stressful. According to the social readjustment rating scale, a list of life events, death of a spouse, marriage, and retirement all feature in the top ten stressful life events (Holmes & Rahe, 1967). Evidence that life events impact immune responses comes from a study which found that bereavement was associated with poorer antibody response to two of the three vaccine strains (H3N2 and B strain) at one month post vaccination (Phillips et al., 2006). On the other hand, marriage was positively associated with vaccine response, with married and cohabiting participants exhibiting higher antibody response to one of the strains than single, separated, widowed or divorced participants. However, this evidence is limited by the use of life event checklists, which are not without their drawbacks. Checklist methods are often associated with inaccurate recall and memory biases, even in relatively short time periods (Raphael, Cloitre, & Dohrenwend, 1991), which, as discussed in section 2.3.2, may be exacerbated by older age. There are also issues surrounding their key assumptions, such as individual differences in what may be considered a life event, as well as what may be considered stressful participants (Brown, 1974; Dohrenwend, 2006).

Discussion

The evidence for the effect of stress on vaccine response is mixed and dependent on the type of stress. Chronic stress appears to be reliably associated with poorer responses to vaccines. The observational evidence certainly suggests that in chronically stressed older adults, immune responses are supressed, either in terms of a slower antibody response or by fewer

antibodies being produced compared to non-stressed individuals, or both. Interventional evidence supports this, by showing that reductions in stress leads to improved antibody responses, although there is some conflicting evidence.

The evidence for acute stress and vaccine response in older adults is less plentiful, with much of the research in this area focusing on younger populations and stressors such as examinations. This evidence suggests that acute stress may have a beneficial effect in terms of vaccine response, however it may depend on the type of stressor. For instance, whilst stress reduction techniques may be beneficial for those exposed to chronic stress, this was not evident for acute exam stress. However, given that the majority of this acute stress research was conducted in young and healthy populations, the applicability to older adults is unknown.

Overall, this evidence seems to mirror the pattern of evidence for stress and immune parameters, discussed in Chapter 2 (section 2.3.1). Chronic stress results in poorer vaccine responses, whereas acute stress may have beneficial effects. Additionally, there seems to be evidence of differential effects depending on the specific virus strain. For instance, H3N2 strains seem to be associated with stress, whereas H1N1 strains have not shown any effect of stress, and evidence for B strains is mixed. The exact reasons for these inconsistencies between strains are unclear, however they may be due to differences in baseline levels in strain specific antibodies. However, many of the studies discussed here do not present this information, and so the interpretation of this evidence is limited. Unfortunately, most of the evidence outlined in this section is further limited by methodological concerns. For

instance, nearly all of the studies discussed here had small sample sizes, which may mean the results are not representative of the population of interest. The small sample sizes also potentially limit the statistical power, and may have led to the inability to detect any effect that was present, exacerbating issues of mixed findings. However, most authors failed to report a power calculation or comment on the power of their studies. Another potential limitation to this research is the heterogeneity in the time at which antibody levels were assessed. This ranged from 2-12 weeks across studies, making comparisons between studies difficult. Peak serum IgG antibody response to influenza vaccination has been established at approximately 2-4 weeks post-vaccination in the older adult population (Gross et al., 1996; Künzel, Glathe, Engelmann, & Van Hoecke, 1996). Therefore, despite the heterogeneity, all of the studies discussed here include at least one measure within that timeframe.

3.3.2 ***Affect***

There is very little direct evidence investigating the role of positive and negative affect in influenza vaccine response in older adults. Therefore, this section will also consider evidence from other vaccines and populations.

3.3.2.1 Negative Affect

As discussed in Chapter 2 (section 2.3.2), negative affect (NA) is often highly conflated with stress, meaning that it can be difficult to disentangle the two constructs in the literature. However, whilst recognising this overlap, some researchers explicitly regard NA as separate from stress (e.g. Pressman et al., 2006). For instance, some researchers suggest that trait NA may increase vulnerability to stress (Costa & McCrae, 1985), demonstrating how the two

constructs are overlapping but distinct. This is further reflected in commonly used mood measures, such as the Profile of Mood States (McNair, 1971) and Positive and Negative Affect Scale (Watson, Clark, & Tellegen, 1988), which do not explicitly include stress, although do include some similar items. Therefore, whilst the previous section discussed the effects of stress and vaccine response, this section considers some additional studies that explicitly consider NA, and not stress.

Studies of influenza vaccine response and NA specifically are limited but do suggest an association between mood and various immune parameters. One study of healthy students given hepatitis B vaccines found that high trait NA predicted lower antibody response (Marsland, Cohen, Rabin, & Manuck, 2001). Similarly, in a study measuring state NA following salmonella typhi vaccination, Wright, Strike, Brydon, and Steptoe (2005) found that negative changes in mood were significantly associated with increases in IL-6 compared to the placebo group, suggesting that NA may impact on inflammatory responses to vaccination. Thus, this suggests that both trait and state NA may influence vaccine responses.

Vaccine response is similarly affected by depression. Glaser, Robles, Sheridan, Malarkey, and Kiecolt-Glaser (2003) studied older adults immediately before and two weeks following the annual influenza vaccination. They found that those with more depressive symptoms had higher levels of baseline IL-6, as well as bigger increases in IL-6 at the follow up. Similarly, a study of older adults receiving the varicella zoster virus vaccine found that those with major depressive disorder had lower levels of cell-mediated

immunity at follow up compared to participants without depression (Irwin et al., 2013).

Together, this evidence suggests that there is a negative association between NA and vaccine response. Further, as the specific measure of vaccine response varies between studies, this suggests that NA may influence a range of immunological parameters. There are limitations to this evidence, however. Studies involving healthy young adults may not be representative of other age groups. Further, the correlational nature of the evidence means that cause and effect cannot be established. Whilst it is likely that NA leads to altered vaccine response, it is also possible that NA may be caused by frequent illness caused by decreased immunocompetence. Thus, NA may be either a cause, or a consequence of impaired immunity. Alternatively, the association between NA and vaccine response may be influenced by confounding factors, such as poor sleep, stress, and loneliness, all of which are associated with negative affect (Marsland et al., 2001; O'Brien et al., 2010; Pressman et al., 2005), as well as independently impacting immune response (some of which is discussed in previous sections). Finally, it is notable that many studies of NA fail to also measure positive affect (PA) which means that, given their overlap, it can be unclear whether the effects seen are caused by increased NA or an absence of PA, or both. Interventional studies are needed to better inform this association, however there are currently no interventional studies of NA and vaccine response.

3.3.2.2 Positive Affect

The association between PA specifically, and in particular state PA, and influenza vaccination response is not well investigated. The limited available

literature, however, does point to trait affect being associated with increased vaccine effectiveness. In a study of older adults given the influenza virus and vaccine, Costanzo et al. (2004) used vigour and optimism as measures of PA. They found that that both measures were associated with greater levels of T-helper type 1 cytokine responses to both the live virus (in particular H1N1 and strain B viruses) and vaccine (strain not specified). However, some would argue that measures such as vigour and optimism should not be used as substitutes for PA, which is its own distinct construct (Pressman & Cohen, 2005). Therefore, whilst this study may be informative regarding the relationship between vigour and optimism, and cytokine response, this may not extend to PA. Nevertheless, results from a study that did use a 'pure' measure of PA show a similar association. In a study of healthy students who were given hepatitis B vaccines, Marsland, Cohen, Rabin, and Manuck (2006) found that higher levels of self-reported trait PA were associated with higher antibody responses to vaccination, and that this association remained after controlling for age, sex and body mass. This association was also still present after controlling for NA. However, given that both studies are observational, they are limited by the issues common to this design previously discussed, including inability to infer causation and potential confounding factors, although both studies did account for most major confounders, improving confidence in the associations observed. However, until recently, no interventional studies specifically investigated the influence of state affect on influenza and/or the older adult population. Therefore, it was unclear whether this association exists in this specific population, whether it can be manipulated, and whether it is limited to trait affect only. The following sections describe the programme of work within which this thesis is based, that started to explore these questions regarding the manipulation of state affect and impact on influenza vaccination in the older adult population.

3.4 The relative importance of psychological factors for intervention targeting

The majority of the research discussed in this chapter thus far has focused on a single psychological factor. Whilst other factors are occasionally controlled for, studies rarely include a comprehensive analysis of these factors as primary factors. Therefore, until recently, the relative importance of each of the psychological factors outlined here had not been well investigated, and the primary factor(s) to target for intervention was unclear. Whilst some studies have considered more than one primary factor, they often are not comprehensive. For instance, Phillips, Burns, Carroll, Ring, and Drayson (2005) investigated stress, as well as behavioural factors including social support,nutrition, sleep and exercise, and found that only stress and social support were associated with influenza vaccine response. However, health behaviours were assessed with single item questions, and other psychological factors such as positive and negative mood were not assessed. Similarly, Kohut, Cooper, Nickolaus, Russell, and Cunnick (2002) assessed optimism and stress, as well as behavioural factors including exercise, multivitamin intake and social activities in older adults, and found that exercise was associated with greater antibody response to influenza vaccination, whilst stress, optimism, multivitamins and social activity were associated with other immune parameters. Again, whilst including multiple factors, this study did not investigate positive and negative mood, thus limiting the ability to assess the relative importance of these psychological factors.

A recent programme of research, in which this thesis is situated, has sought to address this, carrying out one of the most comprehensive studies to date.

Ayling, Fairclough, et al. (2018) conducted a prospective longitudinal observational study of 138 community dwelling older adults in which multiple factors were simultaneously measured, including stress, positive mood, and negative mood, as well as behavioural factors such as nutrition, physical activity and sleep. Participants completed various repeated measures to assess these factors over the two weeks prior to, and four weeks following, receiving the influenza vaccination. Antibody response was assessed at four- and 16-weeks post-vaccination. Results demonstrated that the only significant predictor of enhanced antibody response to vaccination was positive mood on the day of vaccination, although this was only seen for one of the included vaccine strains (H1N1). Whilst this study addressed some issues found in previous research, such as the use of daily measures of mood, reducing the reliance on retrospective measures, and the inclusion of both positive and negative mood measures, it is somewhat limited by the fact that significant effects were only seen for one vaccine strain. This may be related to a ceiling effect caused by high baseline levels of these antibodies (63% and 47% of participants had seroprotective levels of H3N2 and B strains at baseline) as a result of previous vaccinations, which has also been documented by previous research (Ohmit, Petrie, Cross, Johnson, & Monto, 2011; Shapiro et al., 2021). Research has also suggested that such psychological factors may only impact vaccine strains with the weakest host immune response (e.g., Edwards et al., 2010; Edwards et al., 2012). In this study this was the H1N1 strain, therefore may also account for this one strain effect. Overall this study indicates that in the area of influenza vaccine effectiveness specifically, PA may be the most important modifiable factor to target in terms of increasing vaccine effectiveness, however, as noted in section 3.3.2 there are currently very few interventional studies addressing this.

3.5 Enhancing Positive Affect on the Day of Influenza Vaccination: A Feasibility Study

To address this gap in the literature, a feasibility study was carried out in the 2017/18 flu season. The primary aim was to investigate the feasibility of delivering a brief intervention in primary care designed to enhance positive affect at the time of influenza vaccination in older adults. The study also aimed to conduct exploratory analyses of the effects of the intervention on vaccine response by examining the size of the effect on antibodies to help power a future trial (Ayling, Fairclough, Buchanan, Wetherell, & Vedhara, 2019). In this study, 103 older adults were randomised into a positive mood enhancement intervention arm (n=52) or a neutral mood comparator arm (n=51). The development of the positive mood intervention was based on a systematic review of brief mood enhancing interventions (Ayling et al., 2019), as well as public and patient involvement groups. This intervention consisted of a 15-minute video package, which included comedy clips, happy music, positive imagery and jokes. The neutral mood intervention consisted of documentary video clips, neutral music, and images. Participants attended their local GP practice, where they gave saliva and blood samples and completed mood questionnaires, before watching their respective intervention video on their own. Following the intervention, they provided a second saliva sample, completed post-intervention mood questionnaires, and received the standard influenza vaccination. Participants returned at four- and 16-weeks post-vaccination to provide follow-up blood samples.

The results of this feasibility study indicated that those who were in the positive mood condition had significantly increased state positive affect post-

intervention when assessed by two of the three positive affect measures, compared to those in the neutral mood condition, although there was a non-significant improvement on one of the measures in the neutral condition. Both groups also showed non-significant decreases in negative affect. Although there was insufficient power to detect changes in antibodies, the results suggested that there may be an improved vaccine response for those in the positive mood intervention. For instance, although there were no significant differences between groups in influenza specific IgG levels, mean point-estimates favoured the positive mood intervention over neutral control. Salivary IgA also significantly increased in both the positive mood and neutral mood groups from pre- to post-video with no differences between groups.

3.5.1 *Remaining questions and avenues for intervention improvement*

Although this study demonstrated that the positive mood intervention was effective in terms of improving positive mood in this population, several limitations, particularly concerning the control condition, may have influenced the results. The fact that participants in both the positive mood and neutral mood interventions showed improvements in positive and negative mood demonstrates that participants may have found the video clips used in the neutral comparator arm interesting enough to act as a mood enhancer. Secondly, the use of music in the neutral condition may also be problematic, as music often induces some level of emotional response, whether positive or negative (Krumhansl, 1997). Therefore, the neutral control condition may not have been truly neutral, which may have resulted in an attenuation of the difference between the two groups. Further, the use of an active comparator rather than usual care means that the incremental benefit of the intervention compared to standard care cannot be determined.

It is also possible that the effectiveness of the positive mood intervention could be further improved. Choice interventions, for instance, are a form of individualised intervention, that have been defined in this thesis as those that allow participants to actively determine an aspect of their treatment or intervention, such as selecting which type of physical activity they wish to take part in in a study of exercise. Such interventions have previously been shown to be more effective than no-choice interventions at increasing attendance to cancer screenings, improving medication adherence, and reducing anxiety (Eaton & Tieber, 2017; Liang et al., 2016; Myers & Branthwaite, 1992). It could be hypothesised, therefore, that this type of choice-based intervention may have a larger effect on mood than one that was not individualised. This will be considered in detail in Chapter 4.

3.6 Chapter summary

There is a surprising lack of evidence for the older adult population for some of the psychological factors reviewed in this chapter, including both acute stress and affect, where evidence often comes from other populations and/or vaccinations. This paucity of evidence is notable, and in contrast to the body of research demonstrating that older adults often show poorer vaccine response and therefore may benefit most from intervention. Although unclear, the reasons for this lack of evidence may include ethical considerations specific to this population, practical issues such as availability and access, or perhaps because the focus of these studies may not be to increase vaccine efficacy, but rather to use vaccines as a model of real-world disease. Despite this, the evidence that does exist for this population, and that taken from other

populations, clearly demonstrates that the effectiveness of vaccinations can be influenced by a range of psychological factors.

This is potentially of clinical significance, as by identifying these factors, it may be possible to operationalise them to improve vaccine efficacy in this vulnerable population, thus potentially reducing influenza related illness, hospitalisation, and even death. Previous research has demonstrated that when considering multiple factors, including psychological and behavioural factors, positive affect appears to offer the most potential for improving vaccine effectiveness. This finding was then used to develop a brief positive mood intervention, which was tested, and demonstrated that not only was the intervention effective at improving positive mood in older adults at the time of receiving influenza vaccination, but also indicated that this may lead to increases in antibody levels. Thus, this intervention has potential for improving the effectiveness of the influenza vaccination and in doing so, reducing influenza related illness and associated negative outcomes. However, it is important to ensure that this intervention is optimised before a definitive trial. Evidence from other areas suggests that using choice interventions may improve outcomes compared to similar no-choice interventions. This approach also lends itself well to the current intervention, which is easily adaptable to incorporate participant choice by modifying the existing video package. Therefore, the following chapter will systematically review the existing literature on the effectiveness of choice-based interventions to inform whether this approach could be used to enhance the effectiveness of the trialled positive mood intervention, thereby improving vaccine effectiveness.

4 Chapter 4: The effect of choice-based interventions on psychological and retention-related outcomes: A systematic review[1]

4.1 Chapter overview

The previous chapter briefly described a previous feasibility study, which demonstrated that a brief digital intervention was effective in enhancing positive mood in older people prior to receiving their influenza vaccination in primary care. However, it is important to consider whether there might be potential to optimise the intervention to enhance the effect on mood and in turn the opportunity to detect a significant effect on antibody response.

There are several potential ways in which the previously trialled positive mood intervention may be optimised, a number of which were considered. For instance, increasing the duration of the intervention, having participants watch the intervention in groups to create a shared experience, and using live comedy rather than video clips were all options, however, were all discounted as they would not be practical in the context of primary care. Alternative intervention content was also considered (see section 5.6.5 for a description of the intervention content), however given the subjective nature of music and humour, it was important to include variety to appeal to a wide range of people. Providing participants with choice in the intervention content may not only increase the likelihood of content being appealing, but is also practical in

[1] The systematic review with meta-analyses presented in this chapter has been published in Carlisle, S., Ayling, K., Jia, R., Buchanan, H., & Vedhara, K. (2021). The effect of choice interventions on retention-related, behavioural and mood outcomes: a systematic review with meta-analysis. *Health Psychology Review*, 1-37, doi:10.1080/17437199.2021.1962386. This version of the systematic review with meta-analysis had an extended focus and included behavioural outcomes.

a clinical environment. Additionally, the provision of choice in interventions has been associated with a number of improved outcomes. However, this has not fully been explored in the context of mood. Thus, this chapter firstly provides background to understand what choice-based interventions are and why they might lead to positive outcomes. It will then describe the methods used for a systematic review of the evidence for these interventions compared to no-choice interventions. This includes a description of the characteristics and features of choice-based interventions to provide an overview of how these types of studies are currently being carried out by researchers. Meta-analyses are also performed to estimate the effectiveness of these interventions in terms of mood- and retention-related outcomes. Thus, this chapter aims to assess whether choice-based interventions are more effective than no-choice interventions for a range of outcomes, and how they are operationalised.

4.2 Individualisation and Choice

Humour and happiness, as well as both physical and mental health, are not one-size-fits-all constructs. What some individuals find funny, others do not. Similarly, not all treatment options work effectively for all patients (Bishop & Lewith, 2008; Celestin, Edwards, & Jamison, 2009; Pisoni, Cleary, Geers, & Tobey, 1999). Individualised intervention design is an approach that takes into account individual needs and variability in terms of personal preference or relevance (Suhonen, Välimäki, & Leino-Kilpi, 2008). Systematic and meta-analytic reviews have indeed found that this type of intervention can have a range of improved outcomes compared to non-individualised interventions, including behavioural outcomes such as adherence to the care regimen, physical activity, and smoking; health outcomes such as skin health, functional health status and pain; and many more including knowledge, anxiety and

confidence (Krebs, Prochaska, & Rossi, 2011; Lustria et al., 2013; Noar, Benac, & Harris, 2007; Suhonen et al., 2008).

Choice interventions have been defined in this thesis as a specific subset of individualised interventions, which differ slightly in that they allow participants to have an *active role* in determining an aspect of the treatment or intervention. This is contrasted with other individualised interventions which may provide a modified or tailored intervention based on some measured characteristic such as personality, motivation, or coping style. The element of free, active choice may have additional positive consequences for both the individual and intervention.

4.3 The Importance of Choice

The importance that many individuals place in choice is reflected in Western society and culture. The free market economic system promotes choice between products and providers, and young voters are often told to 'choose or lose' to encourage voting (Patall, Cooper, & Robinson, 2008). Indeed, western society is frequently associated with individualism, a construct which places high value in autonomy, freedom and choice (Realo, Koido, Ceulemans, & Allik, 2002). Further, researchers have suggested that in western cultures, choice may act as a vehicle for self-expression, and thus may be deeply intertwined with one's self-identity (Markus & Kitayama, 1991a, 1991b). Therefore, it is not surprising that choice may also be valued in the context of physical and mental health in western cultures.

Control and autonomy are recognised as a key factor in multiple behaviour change theories. According to self-determination theory (Deci & Ryan, 1980;

Ryan & Deci, 2000), autonomy is one of the key factors that underlies intrinsic motivation. Situations in which autonomy is promoted will therefore enhance motivation. This in turn can lead to other positive outcomes such as improved learning, task engagement, perceived competence, and better health (Deci & Ryan, 2012). Similarly, the theory of planned behaviour suggests that perceived control is one of the key components that drives behaviour (Ajzen, 1985). Several studies have demonstrated that both autonomy and perceived control are linked to wellbeing, positive mood and positive attitudes (Grob, 2000; Reis, Sheldon, Gable, Roscoe, & Ryan, 2000; Sheldon, Ryan, & Reis, 1996), as well as being an important component in behaviour change (Terry & O'Leary, 1995; Williams, Freedman, & Deci, 1998). Given that choice may increase both perceived control (Rotter, 1966; Staub, 2013), and autonomy (Dan-Cohen, 1992), it is possible that the very act of allowing choice can lead to both changes in behaviour and mood, regardless of the content. Indeed, choice has been found to increase feelings of personal control, motivation, and interest, even when choices appeared trivial or mundane (Cordova & Lepper, 1996; Swann Jr & Pittman, 1977). In fact, even unpleasant activities, such as eating grasshoppers or administering themselves electric shocks are perceived as less unpleasant when participants felt that they had chosen the activity themselves (Zimbardo, Weisenberg, Firestone, & Levy, 1965).

A further potential benefit of providing choice in intervention design may be the increase in personal relevance and acceptability. As previously noted, not all people like the same things. Therefore, providing choice in terms of which activity to take part in, music to listen to, or type of treatment to undergo, increases the likelihood that at least one of the options will be acceptable to the participant. This may lead to increased engagement, more positive

attitudes, and better mood. Indeed, studies have shown that both personal relevance and choice leads to increased adherence and intervention satisfaction. In a meta-analysis of 34 studies involving either choice of treatment, shared decision making or assessment of patient preference, those who had some degree of choice had higher treatment satisfaction, increased completion rates, and better clinical outcomes in terms of both medical and mental health conditions, compared to those who had no choice or did not receive their preferred treatment (Lindhiem, Bennett, Trentacosta, & McLear, 2014). When participants do not receive their treatment of choice, on the other hand, they may experience negative attitudes, poorer motivation and poorer adherence (Bowling & Rowe, 2005; Bradley, 1993; Torgerson, Klaber-Moffett, & Russell, 1996). Relatedly, the removal or restriction of choice can also have negative consequences, such as diminished motivation (Deci, Connell, & Ryan, 1989; Seligman, 1975), poorer attitudes towards remaining options (Brehm & Sensenig, 1966), reduced engagement and increased drop-out (Bradley 1993; Feine et al, 1998).

While the above points to the many benefits of providing choice in intervention design, there are some circumstances when choice may not be beneficial. Although some argue that when giving choice, all plausible options should be available to participants (Raffle, 2001), others have found that too many choices can lead to poorer decision making and increased difficulty in making decisions (Gourville & Soman, 2005; Iyengar & Lepper, 2000; Schwartz, 2004). Choice has also been associated with a reduced ability to exert self-control, poorer performance and reduced persistence in subsequent tasks (Baumeister, Bratslavsky, Muraven, & Tice, 1998; Bruyneel, Dewitte, Vohs, & Warlop, 2006; Vohs et al., 2004), whilst some research has found that choice may have no effect on motivation, engagement or attrition (Flowerday,

Schraw, & Stevens, 2004; King et al., 2005). Thus, the evidence for the effectiveness of choice interventions is mixed and may depend on how choice interventions are operationalised.

4.4 Factors that might impact choice

There are a number of factors involved in the operationalisation of choice interventions that may impact the effect of choice on various outcomes. The type of choice, number of choices and the type of control group may all influence the impact that choice has.

4.4.1 *Type of choice*

The type of choice used may vary in several respects, including the degree of personal relevance, importance, and effort, as well as the extent of the choice. For instance, evidence suggests that studies that offer choices between pre-specified tasks such as an writing essay about either plants or animals, are less effective than those that allow choices between more meaningful and relevant elements, such as choices relating to the method or goals of a task (Reeve, Nix, & Hamm, 2003; Zuckerman, Porac, Lathin, & Deci, 1978). In a review and meta-analysis on the effect of choice on intrinsic motivation, Patall et al. (2008) defined five categories of choice, including choice between activities (e.g. choice between an essay task or crossword puzzle), choice between versions of an activity (e.g. choice between six categories of anagram), choice between instructionally irrelevant aspects of an activity (e.g. choice between aspects of a computer game such as icon used to display the player), choice between instructionally relevant aspects (e.g. choice between which words to learn in a foreign language), and choice between rewards for the task. Differences were indeed found between the types of choice,

indicating again that the specific parameters regarding choice can affect the impact of choice. Interestingly, instructionally irrelevant choices had the biggest impact on intrinsic motivation. Whilst this contrasts with previous findings that choices that are the most meaningful had better outcomes, the authors suggest that these findings are in line with self-regulation theory, according to which these types of choices are also most effortful. The very act of providing choice may be enough to lead to beneficial outcomes, whilst choice that creates too much autonomy may be too effortful.

4.4.2 *Number of choices*

As previously stated, whilst some argue that more choice is better, others have found that there is such a thing as too much choice. Consistent with the self-regulatory approach, too many options may be overwhelming and thus have negative effects on both motivation and effort (Iyengar & Lepper, 2000; Schwartz, 2000). Alternatively, too little choice could result in frustration, and a decreased experience of choice. In their meta-analysis, Pattall et al. (2008) found that the number of choices moderated the effect of choice on motivation, with greater effects when participants repeatedly chose a single option from a list of options, compared to just a single choice or multiple choices from a single list of options. Further, making two to four choices in a single manipulation was more effective than making a single choice, or five or more choices. Thus, making a single choice may not be sufficient to significantly increase autonomy and, in turn, motivation, whereas too many choices may be too effortful. However, it is unclear whether this applies to other outcomes such as mood, or just motivation.

4.5 Why a Review is Needed

The above discussed literature paints an unclear and, at times, contradictory picture regarding the benefits of choice, and how various aspects of choice might impact on intervention outcomes. Further, much of the literature, including the systematic review evidence, focuses on choice in relation to outcomes such as motivation and learning. There is some evidence to suggest that giving patients a more active role in their treatment may lead to better outcomes, including participant retention and satisfaction, and some clinical outcomes. Indeed, it seems reasonable to expect that choice provision will lead to increased satisfaction. However, it is unclear whether the potential benefits of choice in terms of attrition and satisfaction translate to better outcomes in terms of mood. Therefore, this review seeks to extend previous reviews in a number of ways. Firstly, by assessing mood related outcomes, in addition to retention-related outcomes. Secondly, this review includes a stricter definition of choice. For example, Lindheim et al., (2014) include preference-based studies, which do not involve active participant choice. They also include shared decision making; whilst this does include active choice, is not necessarily the same as free, participant-driven choice. In applying stricter criteria, this review enables a higher degree of confidence that any observed benefits are due to choice alone, and not impacted by other factors, such as the influence of the clinician. Additionally, although frequently used, choice interventions are currently poorly defined in the literature, making such studies difficult to find for researchers wanting to understand how such studies are being conducted. Therefore, this review will also seek to summarise how choice has been operationalised and highlight the differences and similarities in the various approaches to choice-based intervention design.

4.5.1 *Objectives*

The aim of this review is to systematically assess the existing literature on the effect of participant choice on mood- and retention-related outcomes. The objectives of this review are to:

i. Assess the effectiveness of choice-based interventions compared to no-choice interventions on mood-related outcomes.
ii. In trials where it is reported, assess retention-related outcomes of choice-based interventions.
iii. Describe the features of choice-based interventions being used.

4.6 Methods

4.6.1 *Inclusion criteria*

An overview of the population, intervention, comparison, outcomes and study design (PICOS) criteria can be found in Table 1 and are described in more detail below.

4.6.1.1 Participants

Studies involving adults of any age were included. The population was not limited in terms of clinical group. Children under 18 years were excluded. This is because of previous research demonstrating that adults and children may respond differently to choice-based interventions (Patall 2008). The only other criteria that the study population had to meet was the ability to make an *active choice* in terms intervention content. To that end, studies involving populations where the choice was made by a caregiver, carer or other third party, such as studies involving adults with severe dementia or brain injury preventing the ability to make a choice, were excluded.

4.6.1.2 Study design

Only randomised controlled trials (RCTs) were included in this review. These were included because randomised controlled trials are widely considered the gold standard of study design and are least susceptible to bias (Hariton & Locascio, 2018). Non-randomised interventional trials where allocation to groups was done by participant preference were not included. Observational studies with no intervention manipulation were not included.

Table 4.1: PICOS

	Inclusion	**Exclusion**
Population	Adults	Those unable to make a choice Children
Intervention	Choice-based interventions Perceived choice Multicomponent as long as choice was the main element and the only difference between groups	No-choice Choice as the control arm
Comparison	No-choice	Usual care No treatment Choice
Outcomes	Retention Mood	
Study Design	RCT	Non-RCT

4.6.1.3 Intervention

As the focus of this review is on choice-based interventions which, as noted in section 4.2, differ in that they involve the participant playing an active role in individualising their intervention, only those interventions where the participants actively and consciously determined the content of the intervention were included. This included choice or preference-based interventions allowing participants to choose from a limited number of options, as well as interventions that involved a free choice. The primary element of the intervention had to be the provision of choice, and this had to be the **only difference** between the intervention and comparison groups. This was to ensure that results were not contaminated by other non-choice elements of the intervention. Thus, multicomponent interventions could be included so long as the only difference between the two groups was the provision of choice. The aim of the choice arm had to be interventional. This was because studies that used choice as a control were unlikely to show any effect of choice as they were not designed to impact the outcomes, and therefore may bias the results of the review. For instance, France et al. (2013) compared the effectiveness of a website designed to address common blood donor concerns to a website where participants viewed videos of their choice on outcomes such as donation attitude, anxiety and intention. Only studies that included a 'no-choice' comparison group were included, to determine whether giving participants an active role in determining the content of the intervention is more effective than not having that choice. Finally, studies where participants believed they had a choice about the content of the intervention, but actually all participants received the same intervention, or both groups received preferred activities were included, provided that all those in the choice group believed they had chosen an aspect of their intervention, and those in the no-choice group believed they had not.

The exclusion criteria included interventions using methods of individualisation that did not involve participant choice, such as those that assessed participant preference but did not involve active choice, and those that were individualised based on personality, stage of change, participant goals, or as part of cognitive behavioural therapy or counselling. Further, studies where the choice was not explicit, or where it was judged that participants in the choice group were pressured to pick a particular option were excluded, as research has found that the effect of this is significantly different from those that allow autonomous choice (Moller, Deci, & Ryan, 2006). Conference papers, letters, editorials, protocols, unpublished studies and stand-alone abstracts were excluded. Non-English studies and studies published in non-peer reviewed journals such as dissertations were also excluded.

4.6.1.4 Outcomes

To be included in the review studies must have reported outcomes relating to either retention- or mood-related outcomes. A full list of outcomes considered to fall under these categories can be found in Table 4.2.

Table 4.2: Mood- and retention-related outcomes

Outcome Category	Specific Outcome
Mood	Depression
	Distress
	Anxiety
	Positive mood
	Stress
	Negative mood

Outcome Category	Specific Outcome
Retention	Drop-out/attendance/attrition
	Adherence to the intervention
	Satisfaction

4.6.2 ***Search method***

4.6.2.1 Databases

Comprehensive searches of the following databases were conducted to identify potentially eligible studies: Medline; Embase; PsychInfo and PsychArticles.

4.6.2.2 Search terms

Key search terms for all databases included terms relating to choice and individualisation, behaviour change, and mood (see Appendix A). Published search terms were used to identify RCTs for Medline, Embase, and Psychinfo (BMJ, Undated; Eady, Wilczynski, Haynes, & Team, 2008; Higgins, 2015). There are no published RCT search terms for PsycArticles, therefore the terms for PsychInfo were also used in PsycArticles.

4.6.3 ***Data collection***

4.6.3.1 Selection of studies

The search was conducted for all databases from earliest records to the 8th January 2019. All search results were screened by title and abstract against the inclusion and exclusion criteria, for possible inclusion. Studies that appeared to satisfy these criteria based on the titles and abstracts, or where it was unclear, then underwent a full text screening. This was primarily done by

one reviewer, however for studies where there was significant uncertainty, inclusion was discussed with a second reviewer.

4.6.3.2 Data extraction

A data extraction spreadsheet was used to extract and record information from each included study. This included basic study information, participant details, intervention and comparator details, information about the reported outcomes, and the results. The extraction sheet can be found in Appendix B. A second assessor cross-checked data extraction to ensure accuracy.

In order to address the primary objective of the review and describe the features of choice-based interventions, several specific details regarding the choice manipulations were extracted, including a description of the choices, the number of choices, number of options per choice, and total number of options.

Studies that reported additional interventional arms that did not meet the inclusion criteria were included but those arms were not extracted.

4.6.3.3 Assessment of risk of bias

Risk of bias was assessed using the Cochrane Collaboration RoB2 tool (Higgins et al., 2016). Each study was assessed for bias related to the randomisation process, deviations from the intended intervention, missing outcome data, measurement of the outcome and selection of the reported result. A second assessor independently assessed risk of bias, and any discrepancies were discussed until a consensus was reached.

4.6.4 *Data synthesis*

Where applicable, outcomes were meta-analysed using Review Manager 5. Meta-analyses were performed using a random effects model, due to the high degree of variability between studies. Meta-analyses were performed for individual retention- and mood-related outcomes as well as overall analyses for the total effect for the mood outcome types. For instance, an overall negative mood analysis was carried out which included different forms of negative mood such as depression and anxiety. As only two studies reported positive mood outcomes, and these were reported using different types of data (i.e. continuous and dichotomous), an overall positive mood analysis was not possible. However, the results of these two studies are included in this review.

For continuous outcomes, the mean and SD was extracted or calculated to determine the differences in means (MDs) and 95% confidence intervals (CIs). For dichotomous outcomes, the number of people with the outcome and the number of people per group were extracted or calculated if percentages were reported instead to calculate risk ratios with 95% CIs. For outcomes where studies had used different methods of assessment, for example depression as measured using the BDI, Hamilton Depression scale etc., a standardised mean difference (SMD) was used. If the same study included two different measures of the same outcome, only the measure most commonly used by other studies was analysed, to avoid double counting of participants. Similarly, for the analysis of overall mood, if a single study reported two relevant outcomes, for instance both anxiety and depression, the study's primary outcome was selected. If both outcomes were listed as primary, or it was unclear, only the outcome with the most participants reporting was selected. If

both outcomes reported the same number of participants, the outcome most commonly reported by other studies in the meta-analysis was extracted. Finally, if two scales of the same outcome measure differed in the direction, the data was recalculated using methods from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2021).

4.6.4.1 Exploratory subgroup analyses

Exploratory subgroup analyses were performed to assess whether there were differences in the effect of choice, based on the features of the choice-based interventions, including the type of choice, the number of choice opportunities and options, and perceived compared to actual choice. Further, given the focus of this thesis on the older adult population, further subgroup analyses were conducted to assess the differences in the main outcomes between older adults (≥65 years) and younger adults (<65 years).

4.6.4.2 Dealing with missing data

Where outcomes were not sufficiently reported for meta-analyses, authors were contacted to supply this information. When this did not resolve the issue, i.e. due to no response or the data no longer available, outcomes were discussed narratively. Appendix C show details of studies and outcomes that could not be meta-analysed. In total, 11 authors were contacted with requests for additional information. Four responded, of which two were able to supply the information requested.

4.6.5 ***GRADE***

GRADE software was used to assess the overall quality of the evidence for each outcome, taking into account risk of bias assessments, inconsistency caused by heterogeneity, imprecision, and indirectness. To assess overall risk of bias, individual risk of bias judgements for each study contributing to the meta-analysed outcome were weighed, and a judgement was made based on the weighting of each study in the meta-analysis. If the majority of the evidence for the outcome was judged as 'some concerns', according to Higgins et al., (2016), there was judged to be a serious risk of bias. If the majority of the evidence was judged as high risk, the GRADE risk of bias assessment was judged to be a very serious risk of bias. An outcome was downgraded to serious risk of inconsistency where there was significant (I^2=50-74%), and very serious risk where there was very significant (I^2>75%) heterogeneity. Judgements of imprecision were based on the degree of confidence in the pooled effect size, as measured by the confidence intervals. GRADE default minimally important differences (MIDs) were used to judge imprecision (for dichotomous outcomes: and RR of 0.8 and 1.25; for continuous outcomes: +/- 0.5 x mean control group SD). If the confidence intervals crossed one of these values, the outcome was judged as having serious imprecision. If both values were crossed, the outcome was judged as having very serious imprecision. Indirectness could also be judged as 'no risk', 'serious risk' or 'very serious risk', based on whether there were serious or very serious deviations from the protocol in terms of either the population, intervention, or outcome. GRADE assessments were carried out for the main analyses only.

4.7 Results

Figure 4.1 shows the PRISMA flow chart. The search retrieved a total of 37,326 results, and an additional nine records were identified by screening reference lists of identified papers including literature reviews and systematic reviews. After removing duplicates, there were 23860 references, of which 23567 were excluded after reviewing the title and abstract, and 293 underwent a full text screening. Of these, 251 were excluded. Common reasons for exclusion included the comparison group not being a no-choice intervention, there being more differences between the intervention and comparison group than just the choice element, the intervention not involving participant-driven choice, and incorrect study design. Overall, 32 studies were included from 39 papers. Twenty-six reported outcomes relating to retention and 19 reported outcomes related to mood.

4.7.1 ***Included studies***

Details of the included studies are reported in Table 4.3.

4.7.1.1 Participants and setting

There was a total of 10,064 participants across the 32 trials, of which 3505 were randomised to choice-based interventions and 6440 were randomised to no-choice interventions. Two studies (n=119) did not report the number of participants randomly allocated to each study arm. The median sample size of the studies was 86 participants.

There were 12 studies including exclusively participants with physical health conditions such as diabetes, cancer, and heart disease, and four studies

including participants with mental health conditions including depression and anxiety. There were four studies that specifically studied populations with drug, alcohol or smoking problems, and three studying an overweight population. Seven studies involved university students, two studies specifically focused on older adults, and another five studies included participants with a mean age of ≥65 years. Four studies included women only, only two studies included men only.

Seventeen studies were conducted in the USA, three in the UK, three in Canada, three in Australia, and one each in Germany, New Zealand, Belgium, the Netherlands, Israel, and Brazil.

4.7.1.2 Interventions and comparisons

Interventions varied significantly in terms of the type of choices provided, the number of choices and the number of options given to those in the choice groups. All comparison group participants were either assigned to an intervention randomly, or randomly assigned to a choice group participant to receive what that participant chose. A detailed description of the different choice interventions and study designs is presented in the next section.

4.7.1.3 Outcomes

Of the 26 studies included in the meta-analyses, 21 reported an outcome relating to retention, including drop-out, adherence to the intervention, and satisfaction. Eleven studies reported a mood-related outcome, of which four reported anxiety, and three reported depression. Other mood outcomes included nervousness, discomfort, distress, happiness, and arousal.

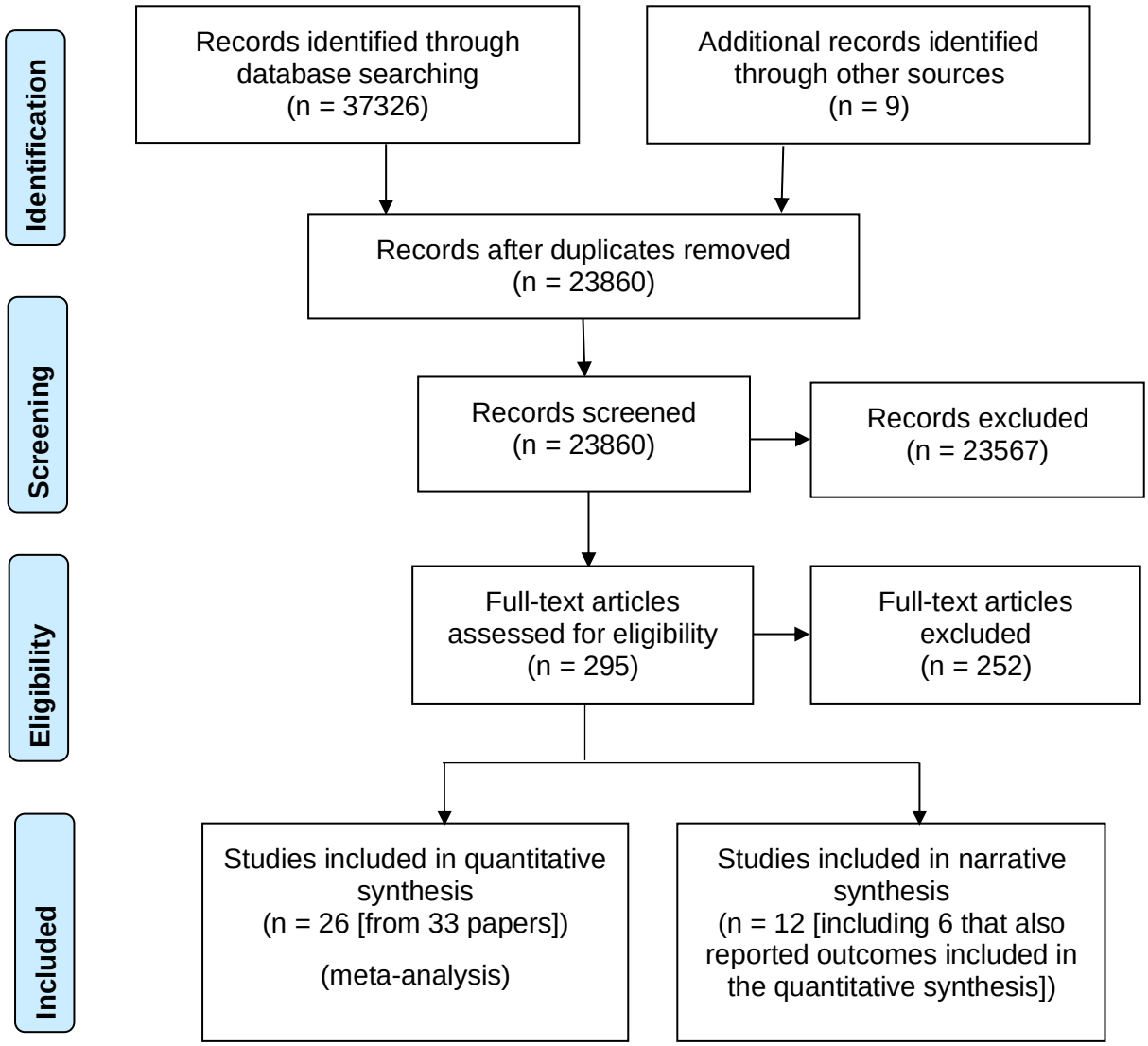


Figure 4.1: PRISMA flow diagram

Table 4.3: Details of included studies

Study	Intervention	Population	Outcome	Comments
Bartley, Faasse, Horne, and Petrie (2016)	**Choice intervention (n=29):** Choice between one of two beta-blockers **No-choice intervention (n=32):** Participants were randomly assigned to one of the two beta-blockers	University students Age (mean, SD): 21.1 (2.78) years 41 females, 20 males New Zealand	At post-test: • Anxiety (Mood)	
Beer, Dimmock, Jackson, and Guelfi (2017)	**Choice intervention (n=29):** Choice of exercise mode (bike or treadmill), exercise intensity, duration of exercise (30-60 min), the time of commencement of the session (0600 – 0900), and the type of music played during exercise, and were provided with cues indicative of choice e.g. ability to change preferences throughout **No-choice intervention (n=29):** Participants underwent exercise session with the parameters chosen by their matched partner	Healthy men and women Age (mean, SD): 22 (4) years 20 females, 38 males Belgium	At immediately post-intervention: • Depression (Mood) • Satisfaction (Retention)	
Borland, Balmford, and Benda (2013)	**Choice intervention (n=758):** Choice between either: • QuitCoach – a personalised, automated tailored cessation program	Smokers and recent quitters	At 7 months: • Drop-out (Retention)	

Study	Intervention	Population	Outcome	Comments
	that generates two- to four-page letters of advice with suggestions about strategy, both actions and ways of thinking, and encouragement • onQ – a programme that provides a series of text messages that include advice and motivation. The user can interact with it by reporting changes (e.g. a quit attempt) so that appropriate stage-specific messages are sent • Both as an integrated package. Participants could change their minds and take up whatever aspects they wanted **No-choice intervention (n=2350):** Participants were assigned to either the QuitCoach, onQ, or the integrated package groups.	Age (mean, range): 42.1 (18-80) years 60% female Australia	• Adherence to intervention (Retention)	
Carey, DeMartini, Prince, Luteran, and Carey (2013)	**Choice intervention (n=147):** Choice between two one-off interventions: • Alcohol101+: interactive CD program with alcohol abuse topics, involves attending a virtual party, decision making, test of knowledge • BMI: intervention session with personalised feedback, estimated typical blood alcohol concentration,	Student drinkers Age (mean, SD): 18.6 (0.71) years 60% male USA	At 1 month: • Drop-out (Retention) • Satisfaction (Retention)	

Study	Intervention	Population	Outcome	Comments
	information about consequences and risk behaviours, personalised goal and tips **No-choice intervention (n=141):** Participants were assigned to either the Alcohol101+ or BMI one-off interventions.			
Chiviacowsky, Wulf, Lewthwaite, and Campos (2012)	**Choice intervention (n=14):** Participants could choose whether to use a balance pole during a balance test. They could request the pole on any of the 10 trials. **No-choice intervention (n=14):** Participants received the balance pole on the same trial as the person they were matched to in the choice group and told that sometimes they would be able to use it, and sometimes not.	People with Parkinson's disease Age (mean): choice group 67.92; no-choice group 66.57. Range 46-88 years 13 females, 17 males Brazil	At immediately post intervention: • Enjoyment (Retention) • Nervousness (Mood)	
Clark (2008)	**Choice intervention (n=496):** Choice between two formats of a programme designed to enhance heart disease management: • Group format: 6-8 women per programme session who met for 2 hours/week for 6 weeks, facilitated by a health educator and peer leader	Women aged >60 years with heart disease Age (mean, range): 72.46 (60-90) years All female	At 18 months: • Drop-out (Retention)	

Study	Intervention	Population	Outcome	Comments
	• Self-directed format: initial 1-hour orientation, then worked at home on an individual basis over 6 weeks to complete the 6 programme units **No-choice intervention (n=391):** Participants were assigned to either group or self-directed formats of the programme	USA		
Goertz, Dominick, Heussen, and vom Dahl (2011)	**Choice intervention (n=100):** Participants could choose one of four options: classical music, relaxing modern music, smooth jazz, and no music **No-choice intervention (n=100):** Participants were assigned to one of the four music groups	Hospitalised patients undergoing elective cardiac catheterization Age (mean, SD): 65 (10) years 63 females, 134 males Germany	At post-intervention (post-operatively): • Anxiety (Mood) • Drop-out (Retention)	
Hack et al. (2003)	**Choice intervention (n=153):** Participant offered choice of receiving audiotape of consultation with oncologist or not **No-choice intervention (n=321):**	Women with a confirmed diagnosis of breast cancer Age (mean, SD): 56.5 (12) years	At 12 weeks post-consultation: • Depression (Mood) • Satisfaction (Retention)	Results could not be meta-analysed

Study	Intervention	Population	Outcome	Comments
	Participant randomised to not be given audio tape, or given audio tape	All female Canada		
Hack, Pickles, Bultz, Ruether, and Degner (2007)	**Choice intervention (n=24):** Participant offered choice of receiving audiotape of consultation with oncologist or not **No-choice intervention (n=48):** Participant randomised to not be given audio tape, or given audio tape	Men with a confirmed diagnosis of prostate cancer Age (mean, SD): 67.4 (7.7) years All males Canada	At 12 weeks post-consultation: • Depression (Mood) • Satisfaction (Retention)	Results could not be meta-analysed
Handelzalts and Keinan (2010)	**Choice intervention (n=24):** Choice of two treatments: • Progressive muscle relaxation: two sessions aiming to reduce physiological arousal. Participants received an audiotape to use at home • Changing of internal dialogue: two sessions of a cognitive behavioural modification technique, aiming to convert negative thought patterns into positive ones **No-choice intervention (n=25):**	Students with test anxiety Age (mean, SD): 24.16 (2.55) years 43 females, 30 males Israel	At 2 months: • Anxiety (Mood)	

Study	Intervention	Population	Outcome	Comments
	Participants were given instructions that led them to believe they were randomly allocated to the treatments when, in actuality, they were allocated according to their preference.			
Harkins, Kullgren, Bellamy, Karlawish, and Glanz (2017)	**Choice intervention (n=30):** Participants could choose between a $20 if they met their goal more than 5 days a week, or $20 for a charity of their choice, or to share between the two. They could choose their option for the coming week each week, for a total of 16 weeks. **No-choice intervention (n=48):** Participants were randomised to receive $20 if they met their walking goal on more than 5 days per week, or to receive $20 for a chosen charity, for a total of 16 weeks.	Adults aged ≥65 years Age (mean): 80.3 years 57 females, 21 males USA	At post intervention (16 weeks): • Drop-out (Retention)	
Hegerl et al. (2010) **Subsidiary papers: Mergl et al., (2011)**	**Choice intervention (n=82):** Participants could select a 10-week treatment with either sertraline or CBT (group format with 5-8 members, 9 sessions at 90 mins each). **No-choice intervention (n=144):** Participants were randomised to either sertraline or CBT.	Primary care patients with depression Age (mean, SD): 46.4 (14.6) years 251 females, 117 males Germany	At end of intervention (10 weeks): • Depression (Mood) • Drop-out (Retention) • Adherence to intervention (Retention)	

Study	Intervention	Population	Outcome	Comments
Inadomi et al. (2012) **Subsidiary papers: Liang et al. (2016)**	**Choice intervention (n=321):** Participants had a choice of FOBT (testing kit given for home administration) or colonoscopy (standard information about procedure and directions for bowel preparation were given). **No-choice intervention (n=676):** Participants were assigned to FOBT or colonoscopy.	Adults at risk of developing colorectal cancer Age (mean, SD): 58.4 (6.9) years 533 females, 464 males USA	At 1 year: • Drop-out (Retention)	
Johnson et al. (2014)	**Choice intervention (n=25):** Teachers could choose between one of two strategies for 6 weeks: • Good behaviour game: a group-contingency classroom management procedure designed to reduce problem behaviour in the classroom • Teacher self-monitoring strategy: not defined Both were similar in terms of time and effort required. **No-choice intervention (n=44):** Participants were assigned to the good behaviour game or teacher self-monitoring for 6 weeks.	Teachers working with kindergarten through sixth-grade students Age not reported 88% female USA	At end of intervention: : • Drop-out (Retention) • Adherence to intervention (Retention)	As 88% in the choice group selected the GBG, those who chose TSM were excluded, and those assigned TSM were excluded

Study	Intervention	Population	Outcome	Comments
Jolly et al. (2011)	**Choice intervention (n=100):** Participants could choose between 6 weight loss interventions (Weight Watchers, Slimming World, Rosemary Conley, Size Down and two primary care programmes – a nurse led one-to-one support in general practice and one-to-one support by a pharmacist). Interventions were 12 weeks. **No-choice intervention (n=540):** Participants were assigned to one of the 6 interventions for 12 weeks.	People registered with general practices with raised BMIs Age not reported 438 females, 202 males UK	At end of intervention (12 weeks): • Adherence to the intervention (Retention) • Drop-out (Retention)	Adherence data could not be meta-analysed
Morris, Edwards, Doyle, and Maconochie (2013)	**Choice intervention (n=191):** Participants could choose between an online questionnaire, being mailed a paper questionnaire, or being interviewed over the phone. **No-choice intervention (n=508):** Randomised to one of the 3 questionnaire versions.	Women who had reported problems conceiving All females Age (mean, SD): 41.7 (6.1) years UK	Time point unclear: • Drop-out (Retention) • Adherence to intervention (Retention)	
Myers and Branthwaite (1992)	**Choice intervention (n=48):** Participants could choose between two medication schedules:	Outpatients with depression	At 12 weeks (end of intervention): • Drop-out (Retention)	Results could not be meta-analysed

Study	Intervention	Population	Outcome	Comments
	• One dose of amitriptyline 75mg or mianserin 30mg at night • 3 doses of amitryptyline 25mg or mianserin 10mg during the day Treatment was for 12 weeks. **No-choice intervention (n=43):** Participants were randomised to one of the two drug routines for 12 weeks.	Age (mean, SD): 45.3 (12.75) years 63 females, 28 males UK		
Noël et al. (1998)	**Choice intervention (n=305):** Participants could choose between two curriculums: • Standard: based on ADA recommendations. Content is 60% non-nutritional management, 40% nutritional management. Includes meal plans and advice to make many dietary changes at once • Experimental: content was 60% nutritional management practices and 40% non-nutritional management. Recommends use of food pyramid instead of meal plan for gradual changes to diet 5 weekly sessions lasting 2 hours. **No-choice intervention (n=291):**	Adults with type 2 diabetes Age (mean, SD): 50.7 (10.9) 62.8% female USA	At 6 months: • Drop-out (Retention) At end of intervention (5 weeks) • Adherence to intervention (Retention)	Drop-out data could not be meta-analysed

Study	Intervention	Population	Outcome	Comments
	Participants were randomised to one of the two curriculums.			
Olson, Schmidt, Winkler, and Wipfli (2011)	**Choice intervention (n=30):** Participants could choose between 7 target health behaviours (oral hygiene, hand hygiene, fruit and veg consumption, sweet consumption, whole milk and red meat consumption, transportation safety, exercise). Participants either had self-management skills training or no self-management skills training. **No-choice intervention (n=30):** Participants had no-choice of target behaviour, and either received or didn't receive self-management skills training. Participants were yoked so the behaviour they were assigned to depended on what the choice group picked.	Employees of a large university and teaching hospital and residents from the neighbouring community Age (mean, SD): 31.1 (9.52) years 51 females, 9 males USA	At the end of intervention (2 weeks): • Adherence to intervention (Retention)	
Patall and Leach (2015)	**Choice intervention (n=50):** Participants were asked if they would rather play a word game or maths game, and whether they would like the difficulty to be all at medium, or a mixture of easy, medium and difficult. Additionally, participants were told that they could work on the puzzles in any	College students Age (range): 18-28 years 70 females, 30 males USA	At the end of intervention: • Satisfaction (Retention)	

Study	Intervention	Population	Outcome	Comments
	order and take as much or as little time as they wanted. **No-choice intervention (n=50):** Participants were assigned to either the word or maths game, and the difficulty assortment. Additionally, participants were told that they should work on the puzzles consecutively and to keep track of their time.			
Pearson, Maddern, and Hewett (2005)	**Choice intervention (n=100):** Participants could choose to watch a video or not. The video contained information on 1) the purpose of the procedure, 2) preparing for a colonoscopy, 3) the procedure itself, 4) potential complications, and 5) the postoperative period. **No-choice intervention (n=99):** Participants were randomised to watch the same video or not.	Consecutive patients scheduled to undergo colonoscopy Age (mean, SD): choice group video: 59.8 (13.5), Choice no-video: 59.7 (14.6); no-choice video 57.2 (15.4); no-choice no video 58.6 (15.8) 79 males Australia	At one week (immediately before procedure): • Anxiety (Mood) • Satisfaction (Retention) • Drop-out (Retention)	Mood outcome could not be meta-analysed
Rokke, Tomhave, and Jocic (1999)	**Choice intervention (n=15):** Choice between two treatments	Older adults with depression	At end of treatment (10 weeks): • Depression (Mood)	Depression data could not be meta-analysed

Study	Intervention	Population	Outcome	Comments
	• Self-Management Therapy (SMT) behavioural target: 10 weekly hour-long individual sessions, focused on self-monitoring, self-evaluation, and self-reinforcement, with a focus on activity change • SMT cognitive target - same format, and same 3 components, but focused on participant thought **No-choice intervention (n=20):** Participants were yoked to the choice group participants.	Age (mean, SD): choice group: 68 (5.7); no-choice group 63 (3.3) 15 females, 25 males USA	• Drop-out (Retention)	
Rose, Geers, Fowler, and Rasinski (2014)	**Choice intervention (n=27):** Participants could choose one of the two treatments (looking at a blue or a green colour). They were told these would reduce discomfort when listening to aversive sounds. **No-choice intervention (n=25):** Participants were told the treatment had been chosen for them and were randomly assigned to one of the two colours.	Undergraduate students Age not reported Gender not reported USA	At immediately post-manipulation: • Discomfort (Mood)	
Rose, Geers, Rasinski, and Fowler (2012)	**Choice intervention (n=not reported):** Participants could choose one of two products (inert ointments that were described	Undergraduate students Age not reported	At immediately post-manipulation: • Anxiety (Mood)	Results could not be meta-analysed

Study	Intervention	Population	Outcome	Comments
	as pain-relieving ointments) to try during a cold pressor task. **No-choice intervention (n=not reported):** Participants randomly assigned to one of the two products.	25 females, 16 males USA		
Rotton and Shats (1996)	**Choice intervention (n=not reported):** Choice of 4 out of 20 movies to watch. Movies were humorous or serious, and some participants read an article describing the benefits of humour whereas some read an article about the benefits of exciting movies. **No-choice intervention (n=not reported):** Participants were yoked to choice participants and they were asked to watch a movie that a choice participant had selected.	Patients about to have orthopaedic surgery Age (mean, SD): 43.03 (9.84) years 39 females, 39 males USA	At immediately post intervention (2-days post-surgery): • Distress (Mood)	Results could not be meta-analysed
Scott et al. (2004)	**Choice intervention (n=62):** Participants were offered a choice of screening methodology: • Colonoscopy • Computed tomographic colonography **No-choice intervention (n=122):** Participants were randomised to received either colonoscopy or CT colonography.	Adults from the general community who were asymptomatic and average-risk Age: Between 50-54 years – 49.5%; between 65-69 years 93 – 50.5%	At immediately following the procedure: • Satisfaction (Retention)	Results could not be meta-analysed

Study	Intervention	Population	Outcome	Comments
		69 females, 115 males USA		
Silberman (2007)	**Choice intervention (n=36):** Participants had choice of 4 positive interventions that they believed would bring the most pleasure, engagement and meaning to their lives. **No-choice intervention (n=36):** Participants were matched based on depression scores to a participant in the choice group, and received the same intervention as their choice group partner chose.	Undergraduate students Age (mean, SD): Choice group: 19.7 (1.2); no-choice group: 19.6 (1.1) 41% male USA	At 1 week: • Happiness (Mood) • Drop-out (Retention)	
van Weert et al. (2005)	**Choice intervention (n=40):** Patients could compose their own program from four components (individual exercise, sports, information and psychoeducation), as judged beneficial to them. The programme was 15 weeks. **No-choice intervention (n=41):** Participants received all 4 components in a 15-week programme.	Cancer survivors with different diagnoses Age (mean, SD): 51.6 (9.3) 84% female Netherlands	At the end of the intervention (15 weeks): • Emotional problems (Mood) • Satisfaction (Retention) • Drop-out (Retention)	Mood and satisfaction data could not be meta-analysed 80% of choice participants selected all 4 components

Study	Intervention	Population	Outcome	Comments
Veitch and Newsham (2000) **Subsidiary papers: Veitch and Newsham (1998)**	**Choice intervention (n=30):** Participants could choose the lighting setting for the day that they would be working under. **No-choice intervention (n=30):** Participants worked under the lighting conditions chosen by their yoked partner in the choice condition. At the end of the day, they were asked what lighting conditions they would have preferred, but they were unaware that other participants had selected the lighting for the day.	Office workers Age (range): 18-62 All female Canada	At immediately post-manipulation: • Pleasure (Mood) • Satisfaction (Retention)	
Wallston et al. (1991)	**Choice intervention (n=37):** Participants were told that they could choose which of 3 standard antiemetic regimens they would prefer having for four chemotherapy sessions. Each was described including possible side effects. **No-choice intervention (n=37):** Participants were given an antiemetic based on the choice of their yoked partner in the choice condition.	People undergoing chemotherapy Age (mean, range): 51.9 (25-78) years 62% female USA	At end of intervention (after 4 sessions): • Anxiety (Mood)	Results could not be meta-analysed
Yancy et al. (2015)	**Choice intervention (n=105):** Participants could choose one of two diets for 48 weeks. They were advised which diet	Outpatients with a body mass index of at least	At end of intervention (48 weeks): • Public distress (Mood)	

Study	Intervention	Population	Outcome	Comments
Subsidiary papers: McVay et al. (2014), McVay et al. (2016)	would best fit their preferences based on a questionnaire. **No-choice intervention (n=102):** Participants were assigned to a diet for 48 weeks.	30 kg/m2 Age (mean, SD): 55 (11) 27% female USA	• Drop-out (Retention) • Adherence to intervention (Retention)	
Zoellner, Roy-Byrne, Mavissakalian, and Feeny (2019) **Subsidiary papers: Le, Doctor, Zoellner, and Feeny (2014)**	**Choice intervention (n=97):** Choice between two PTSD treatments: • Prolonged exposure: the psychotherapy was delivered in 10 weekly 90-to 120-minute sessions according to a manual • Sertraline: participants met with a psychiatrist for ten 30-minute weekly sessions. The dosage was started at 25mg/day with the goal of 200 mg/day **No-choice intervention (n=103):** Participants were randomised to either prolonged exposure therapy or sertraline.	People with post-traumatic stress disorder Age (mean SD): 37.41 (11.30) years 75.5% female USA	At the end of the intervention (10 weeks): • Anxiety (Mood) • Adherence to intervention (Retention) • Drop-out (Retention)	

4.7.2 ***Features of choice-based interventions***

4.7.2.1 Number of choices and options

Three of the 32 studies included more than one choice opportunity. For instance, the intervention outlined in Beer, Dimmock, Jackson, and Guelfi (2017) involved participants choosing the mode of exercise, exercise intensity, duration of exercise, time of the exercise session, and type of music playing during the exercise. The majority of studies included two options per choice, although 10 included more, with 20 being the maximum number of options offered.

4.7.2.2 Choice type

The choice interventions also differed by the type of choice offered. Whilst the specific content of the interventions varied widely between studies, it was possible to group the type of choice according to six broad categories. A brief description of these categories and an example from the included studies can be found in Table 4.4.

Whilst the most commonly used type of choice was ‘same classification’, it is worth noting that within this category there was variation in the specific interventions. For instance, seven studies related to choice between programmes targeting specific behaviours or medication conditions, some of which differed in the format (i.e. group versus individual), whereas others differed in their specific content or focus (i.e. behaviour change versus cognitions). Three studies related to choices between pharmacological agents, two involved choices between placebo treatments, two involved choice between diets, two related to choices between music or films, one related to screening methodologies, one involved choices regarding the

environmental conditions, one related to the method of questionnaire delivery, and one related to choices regarding reminder strategies. Thus, within this broad category, there was a lot of variation in terms of the specific type of choices offered.

Table 4.4: The six choice categories with examples

Type of choice	Description	Example
Same class	Different versions of the same/similar intervention	One of two diets: a low-carbohydrate diet or a low-fat diet
Different class	Two or more distinct interventions	Psychological therapy (prolonged exposure) or pharmacological therapy (sertraline)
Having or not	Offered to have something or not	Audiotape of the participants' doctor consultation or no audiotape
Incentive	Choice of reward for carrying out a specific behaviour	$15 gift-card or entry into a lottery for $40 if participants obtained a mammogram
Other	Does not fit into the above categories	One of seven health behaviours to target for improvement
Combination	Combination of the above categories	Choice of exercise mode, exercise intensity, duration of exercise, time of commencement and music whilst exercising

4.7.2.3 Design

There were three categories of study design. Firstly, standard RCT (n=13; resulting in a 2:1 participant allocation), secondly a two-step RCT (n=11) where participants were firstly randomised to either a choice or no-choice condition, and those in the no-choice condition were further randomised to

one of the various no-choice conditions (resulting in a 1:1 allocation). Lastly, a matched design, where participants are randomised to a choice or no-choice condition, and then participants in the no-choice group are yoked, or matched, to a participant in the choice group (n=8).

4.7.2.4 Actual or perceived choice

One of the included interventions involved perceived manipulation of no-choice, rather than actual no-choice. In this study, Handelzalts and Keinan (2010) gave participants in the no-choice group instructions that led them to believe that they were randomly allocated to one of two interventions, when in fact participants were allocated according to preference. To test whether the choice manipulation worked, the authors measured feelings of control, and found that those in the choice group had significantly higher levels of perceived control compared to the no-choice group ($M = 3.04$, $SD = 0.86$; $M = 2.52$, $SD = 0.71$; $p < .05$). Additionally, Patall and Leach (2015) gave the participants in choice group several choice opportunities, one of which included the choice of task difficulty. Participants in the no-choice group were told that they were assigned to a task difficulty. In fact, all participants received the same difficulty level, regardless of choice or assignment. This study also showed that those in the choice group had significantly higher perceived choice opportunities than those in the no-choice group ($M = 5.15$, $SD = 0.95$; $M = 4.47$, $SD = 1.19$; $p = .001$).

The characteristics of the 32 included choice interventions are outlined in Table 4.5.

Table 4.5: Characteristics of choice interventions

Study	No. of Choices	No. of Options	Choice Type	Design	Actual or Perceived
Bartley et al. (2016)	1	2	Same class	Two step RCT	Actual
Beer et al. (2017)	5	Unclear	Combination	Yoked	Actual
Borland et al. (2013)	1	3	Same class	Two step RCT	Actual
Carey et al. (2013)	1	2	Same class	Two step RCT	Actual
Chiviacowsky et al. (2012)	1	2	Having or not	Yoked	Actual
Clark et al. (2008)	1	2	Same class	RCT	Actual
Goertz et al. (2011)	1	3	Same class	Two step RCT	Actual
Hack et al. (2003)	1	2	Having or not	RCT	Actual
Hack et al. (2007)	1	2	Having or not	RCT	Actual
Handelzalts and Keinan (2010)	1	2	Different class	RCT	Perceived
Harkins et al. (2017)	1	3	Incentives	RCT	Actual
Hegerl et al. (2010)	1	2	Different class	RCT	Actual
Inadomi et al. (2012)	1	2	Same class	RCT	Actual
Johnson et al. (2014)	1	2	Different class	RCT	Actual
Jolly et al. (2011)	1	6	Same class	RCT	Actual
Morris et al. (2013)	1	3	Same class	RCT	Actual

Study	No. of Choices	No. of Options	Choice Type	Design	Actual or Perceived
Myers and Branthwaite (1992)	1	2	Same class	RCT	Actual
Noël et al. (1998)	1	2	Same class	Two step RCT	Actual
Olson et al. (2011)	1	7	Other	Yoked	Actual
Patall and Leach (2015)	3	Unclear	Combination	Two step RCT	Mixed
Pearson et al. (2005)	1	2	Having or not	Two step RCT	Actual
Rokke et al. (1999)	1	2	Same class	Yoked	Actual
Rose et al. (2014)	1	2	Same class	Two step RCT	Actual
Rose et al. (2012)	1	2	Same class	Two step RCT	Actual
Rotton and Shats (1996)	4	20	Same class	Yoked	Actual
Scott et al. (2004)	1	2	Same class	RCT	Actual
Silberman (2007)	1	4	Same class	Yoked	Actual
van Weert et al. (2005)	1	4	Same class	RCT	Actual
Veitch and Newsham (2000)	1	4	Same class	Yoked	Actual
Wallston et al. (1991)	1	3	Same class	Yoked	Actual
Yancy et al. (2015)	1	2	Same class	Two step RCT	Actual
Zoellner et al. (2019)	1	2	Different class	Two step RCT	Actual

4.7.3 ***Effects of the interventions***

Of the 32 included studies, 26 were included in the meta-analyses. Meta-analyses are presented for retention-related outcomes, as well as the combined total mood outcome.

4.7.3.1 Studies that could not be meta-analysed

Six studies could not be included in the meta-analysis as they did not provide enough information and either did not respond to attempts to make contact, or the requested data was no longer available. Additionally, six studies that were included in the meta-analysis reported other relevant outcomes that could not be included for the same reason. Details of the outcomes that could not be meta-analysed can be found in Appendix C.

4.7.3.2 Narrative findings of studies that could not be meta-analysed

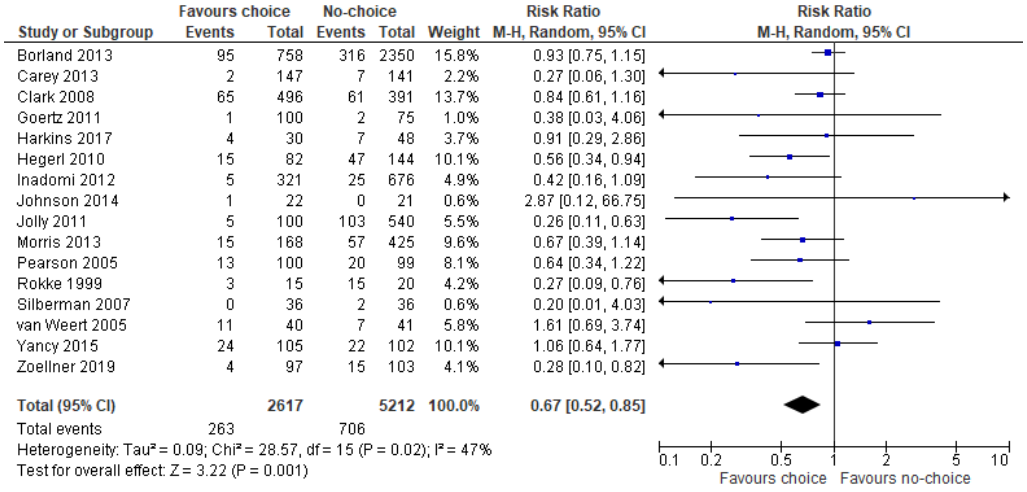
Of the 12 studies reporting outcomes that could not be meta-analysed, only two studies reported enough outcome information to be discussed narratively. Rokke et al. (1999) reported outcomes for depression according to four methods of assessment, all of which found no significant differences between groups. Rose et al. (2012) reported anxiety, and found that mean values were lower in the choice group compared to the no-choice group.

4.7.3.3 Results of the meta-analysis: Retention-related outcomes

Studies reported retention-related outcomes in several ways. The most commonly reported retention-related outcome was drop-out. Of the 16 studies reporting this outcome, 13 favoured choice and three favoured no-choice

(Figure 4.2). Overall, the weighted point-estimate favoured choice with an effect size of RR 0.67 (95% CI 0.52-0.85), which was statistically significant (p= .001). Using the GRADE criteria, the quality of the evidence for this outcome was low, due to risk of bias and some imprecision around the point estimate. Analyses of anticipated absolute effects showed that the risk of drop-out in the no-choice groups was 146 participants per 1000, whereas in the choice groups there were 48 fewer dropouts per 1000 (Table 4.6).

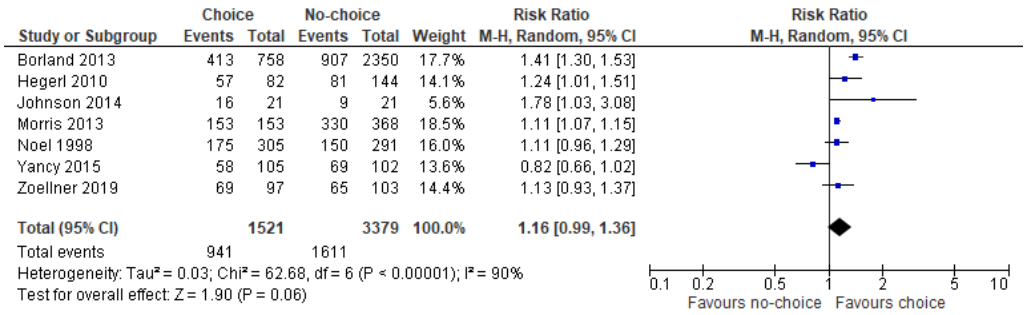
Figure 4.2: Drop-out



Seven studies reported adherence to the intervention at the end of the intervention (Figure 4.3). Six of these favoured choice interventions, and one favoured no-choice. The overall weighted point-estimate favoured choice with an effect size of RR = 1.16 (95% CI 0.99-1.36), however this was not statistically significant. The quality of evidence for this outcome was very low, due to risk of bias, imprecision and significant heterogeneity, which was not explained by any subgroup analyses. In terms of absolute effects, the number of adherent participants without a choice was 563 per 1000, with 90 more adherent participants in choice groups per 1000, compared to no-choice

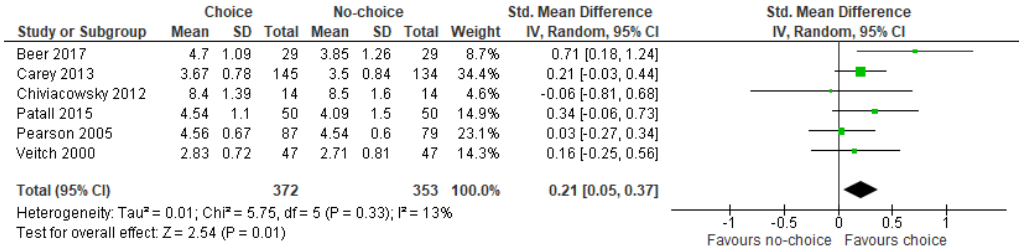
interventions. Additionally, one study reported adherence on a continuous scale, in terms of the percentage of compliance with the intervention, and found that adherence was higher in choice compared with no-choice groups (61.7% versus 43.4%; MD 18.30, 95% CI 2.78-33.82; Olson et al., 2011).

Figure 4.3: Adherence



Six studies also reported the outcome satisfaction, which was measured in terms of enjoyment and satisfaction (Figure 4.4). Of these six, five favoured choice, with the overall point-estimate also significantly favouring choice with a standardised mean difference of 0.21 (95% CI 0.05-0.37, p = 0.01). The quality of this evidence was low, due to risk of bias. Anticipated absolute effects showed a risk difference of 0.21 standard deviations higher in the choice group compared to the no-choice groups.

Figure 4.4: Satisfaction



Beer 2017: The intrinsic motivation inventory – enjoyment subscale; Carey 2013: client satisfaction based on a 5-point likert scale; Chiviacowsky 2012: single item regarding enjoyment; Patall 2015: Interest-enjoyment subscale of the Intrinsic Motivation inventory; Pearson 2005: patient satisfaction based on a 5-point likert scale; Veitch 2000: Environmental Satisfaction scale

Table 4.6: Evidence summary: Retention

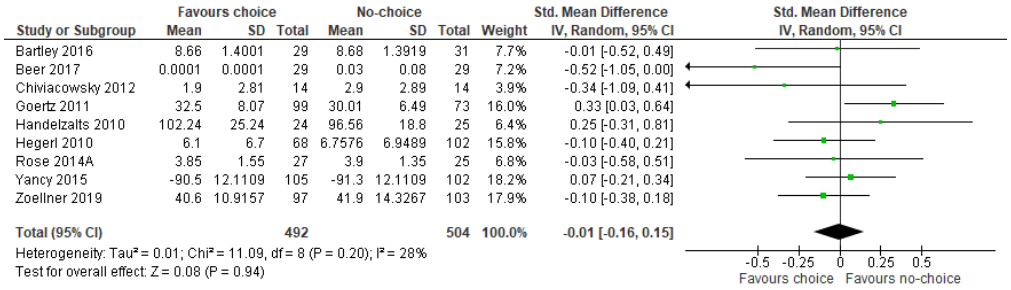
Outcomes	**No of participants (studies)**	**Quality of the evidence (grade)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with no-choice	**Risk difference with choice (95% CI)**
Drop-out	7829 (16 studies)	⨁⨁⨀⨀ **LOW**[1] due to risk of bias, imprecision	**RR 0.67** (0.52 to 0.85)	**Moderate** **146 per 1000**	**48 fewer per 1000** (from 22 fewer to 70 fewer)
Adherence to intervention	4900 (7 studies)	⨁⨀⨀⨀ **VERY LOW**[1,2,3] due to risk of bias, inconsistency, imprecision	**RR 1.16** (0.99 to 1.36)	**Moderate** **563 per 1000**	**90 more per 1000** (from 6 fewer to 203 more)
Satisfaction (enjoyment; interventional satisfaction)	725 (6 studies)	⨁⨁⨁⨀ **MODERATE**[1] due to risk of bias	-	-[4]	The mean score in the intervention groups was **0.21 standard deviations higher** (0.05 to 0.37 higher)

[1] Downgraded once if the majority of studies were judged as having some concerns, and twice if the majority of studies were high risk of bias
[2] Downgraded once for serious heterogeneity (50-74%) and twice for very serious heterogeneity (>75%)
[3] Downgraded once for serious imprecision and twice for very serious imprecision
[4] Could not be calculated as standardised mean difference

4.7.3.4 Results of the meta-analysis: Mood

A total of 11 studies reported a total of eight different mood outcomes. For the purposes of the review, and given the similarity of the different outcomes concerning negative mood states, studies reporting a measure of negative mood were analysed together. This analysis included nine studies, of which six favoured choice and three favoured no-choice (Figure 4.5). Overall, the weighted point-estimate showed no difference between groups, with a SMD of -0.01 (95% CI -0.16-0.15, p = .94). The quality of the evidence for this outcome was low, due to risk of bias. Analyses of anticipated absolute effects showed that with choice interventions, scores were 0.01 standard deviations lower than no-choice interventions, where low score represent better outcomes (Table 4.7). One of the included studies reported a mean and SD of zero in the choice arm (Beer et al., 2017). A sensitivity analysis, removing this study to assess the effect of this study on the overall analysis resulted in a SMD of 0.04 (95% CI -0.09-0.17, p = .58; Appendix D). Additionally, one study reported depression in terms of the number of participants experiencing an increase in depression and found a non-significant benefit of choice (RR 0.82, 95% CI 0.57-1.19; Silberman 2007).

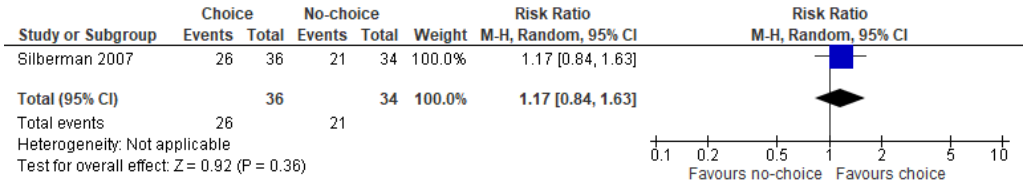
Figure 4.5: Negative mood



Note: Bartley 2016: short-form State-Trait Anxiety Inventory; Beer 2017: Profile of Mood States – Adolescent Inventory; Chiviacowsky 2012: non-validated questionnaire; Goertz 2011: State-Trait Anxiety Inventory – State; Handelzalts 2010: Sarason's Test Anxiety; Hegerl 2010: Hamilton Depression Rating Scale; Rose 2014A: aggregated likert scales for irritated, uncomfortable and unpleasant; Yancy 2015: Impact of Weight on Quality of Life-Lite questionnaire – distress subscale; Zoellner 2019: Spielberger State-Trait Anxiety Inventory

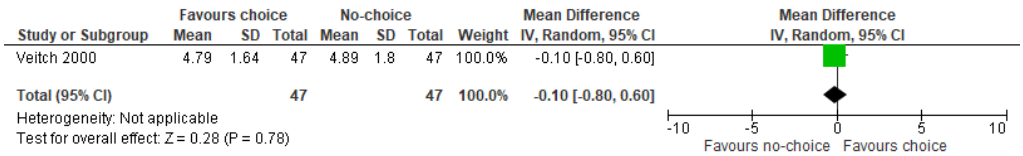
Two studies reported measures of positive mood. One study reported positive mood in terms of the number of people experiencing an increase in happiness (Figure 4.6). This study favoured choice, with an RR of 1.17 (95% CI 0.84-1.63). Whilst this was not statistically significant (p = .36), it equates to 105 more participants per 1000 experiencing an increase in happiness compared to the no-choice group, in which the anticipated number of participants with this outcome was 618 per 1000. However, this evidence is very low quality, due to risk of bias and imprecision.

Figure 4.6: Number of people experiencing happiness



One study reported positive mood in terms of pleasure (Figure 4.7). This study favoured no-choice, with a MD of -0.10 (95% CI -0.87-0.60), however this was not statistically significant (p = .78). The quality of this evidence was moderate, due to risk of bias.

Figure 4.7: Pleasure



Note: Assessed using an 18-item mood questionnaire (Russell & Mehrabian, 1977) - pleasure subscale extracted

Table 4.7: Evidence summary: Mood

Outcomes	No of participants (studies)	Quality of the evidence (grade)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no-choice	Risk difference with choice (95% CI)
All negative mood	938 (9 studies)	⨁⨁⨀⨀ **LOW**[1] due to risk of bias	-	-[4]	The mean total negative mood score in the intervention groups was **0.04 standard deviations higher** (0.09 lower to 0.17 higher)
Pleasure	90 (1 study)	⨁⨁⨁⨀ **MODERATE**[1] due to risk of bias	-	The mean pleasure score in the control groups was **4.89**	The mean pleasure score in the intervention groups was **0.1 lower** (0.87 lower to 0.67 higher)
Increase in happiness	70 (1 study)	⨁⨀⨀⨀ **VERY LOW**[1] due to risk of bias, imprecision	**RR 1.17** (0.84 to 1.63)	**Moderate** **618 per 1000**	**105 more per 1000** (from 99 fewer to 389 more)

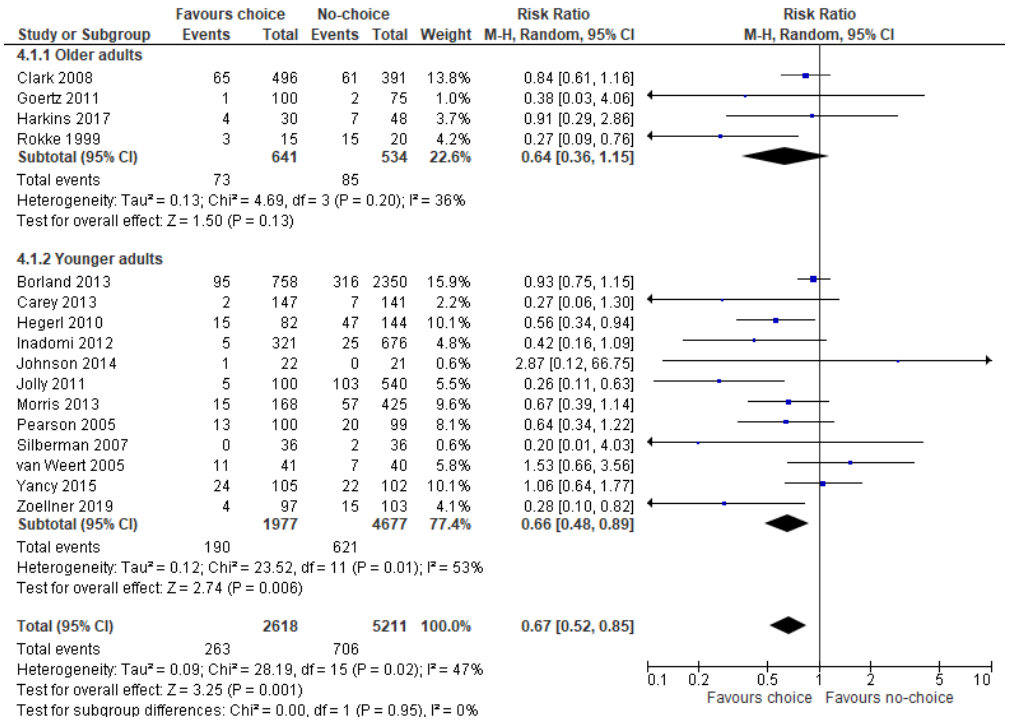
[1] Downgraded once if the majority of studies were judged as having some concerns, and twice if the majority of studies were high risk of bias
[2] Downgraded once for serious heterogeneity (50-74%) and twice for very serious heterogeneity (>75%)
[3] Downgraded once for serious imprecision and twice for very serious imprecision
[4] Could not be calculated as standardised mean difference

4.7.3.5 Results of the meta-analysis: Exploratory subgroup analyses

Older adults

Of the seven studies that either included an older adult population specifically or had a mean participant age of 65 years or older, five reported an outcome that could be included in the meta-analyses, the most common of which was drop-out. The analyses, seen in Figure 4.8, showed that for the older adult age group, the weighted point-estimate favoured choice with an effect size of RR 0.64 (95% CI 0.36-1.15), however this was not statistically significant (p = .13). This was similar to the effect size observed for younger adults (RR 0.66, 95% CI 0.48-0.89), which was statistically significant (p = .006), and the overall population described in section 4.7.3.3. Mood was also reported by two studies with an older adult population, however given the very small number of studies, subgroup analyses were not considered informative and were not carried out.

Figure 4.8: Drop-out in according to participant age



Features of choice-based interventions: Type of choice

Subgroup analyses according were carried out to compare the different types of choice used in each study. In terms of drop-out, analyses showed that all subgroups favoured choice (Figure 4.9). The largest effect size was seen for the 'difference class' category, which favoured choice and was also statistically significant (RR 0.50, 95% CI 0.27-0.92, p = .03). There were also significant effects for the 'same class' category (RR 0.69, 95% CI 0.51-0.93, p = .02). Figure 4.10 showed that in terms of adherence, different class interventions had the largest effect size and significantly favoured choice (RR 1.22, 95% CI 1.04-1.43, p = .02), whereas for satisfaction, combination studies had the largest effect size significantly favouring choice (Figure 4.11; SMD 0.48, 95% CI 0.13-0.84, p = .008).

Of the studies reporting a mood outcome, four used the same class of choice, three used a different class of choice, and one used a combination of choices. As seen in Figure 4.12, the combination category had the largest effect size favouring choice (SMD -0.52, 95% CI -1.05-0.00, p = .05), however this was based on a single study reporting a mean and SD of zero in the choice arm.

Figure 4.9: Drop-out by type of choice

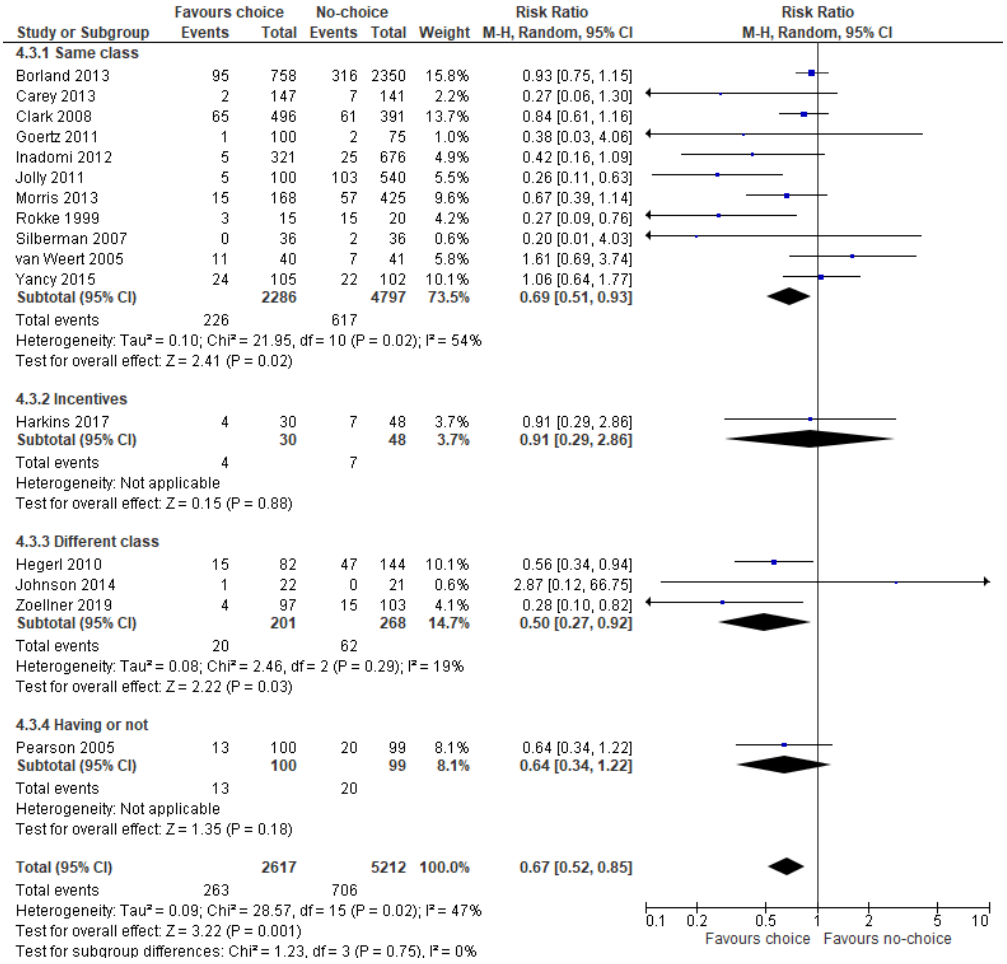


Figure 4.10: Adherence according to type of choice

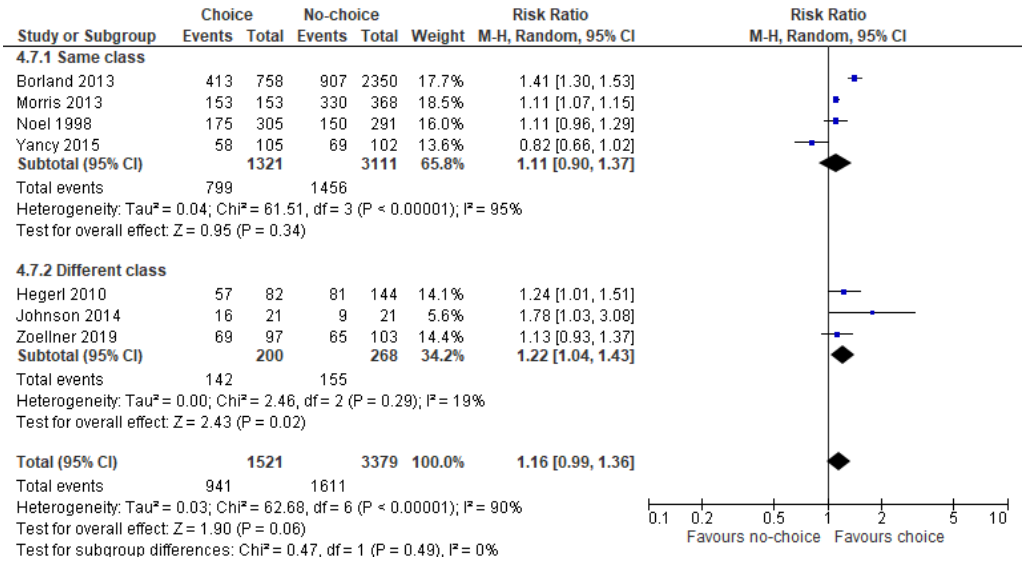


Figure 4.11: Satisfaction according to type of choice

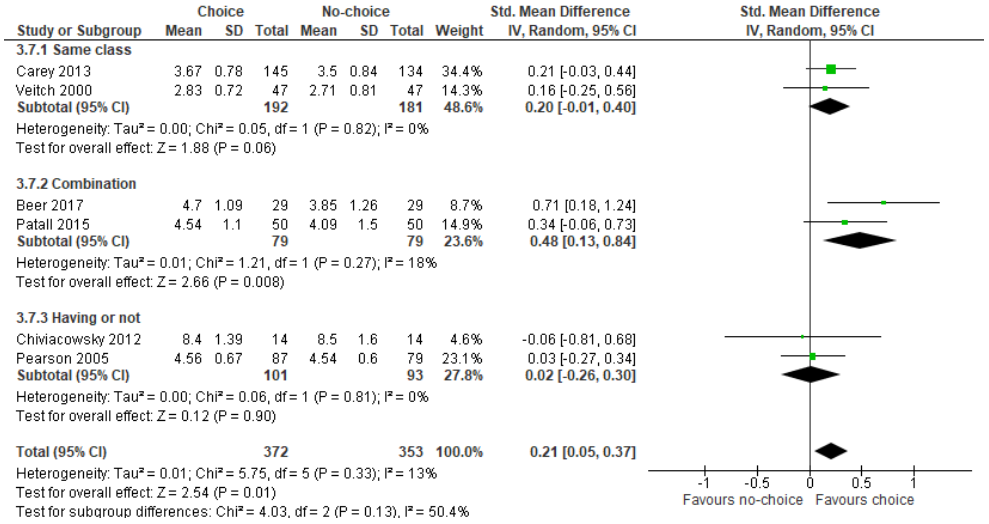
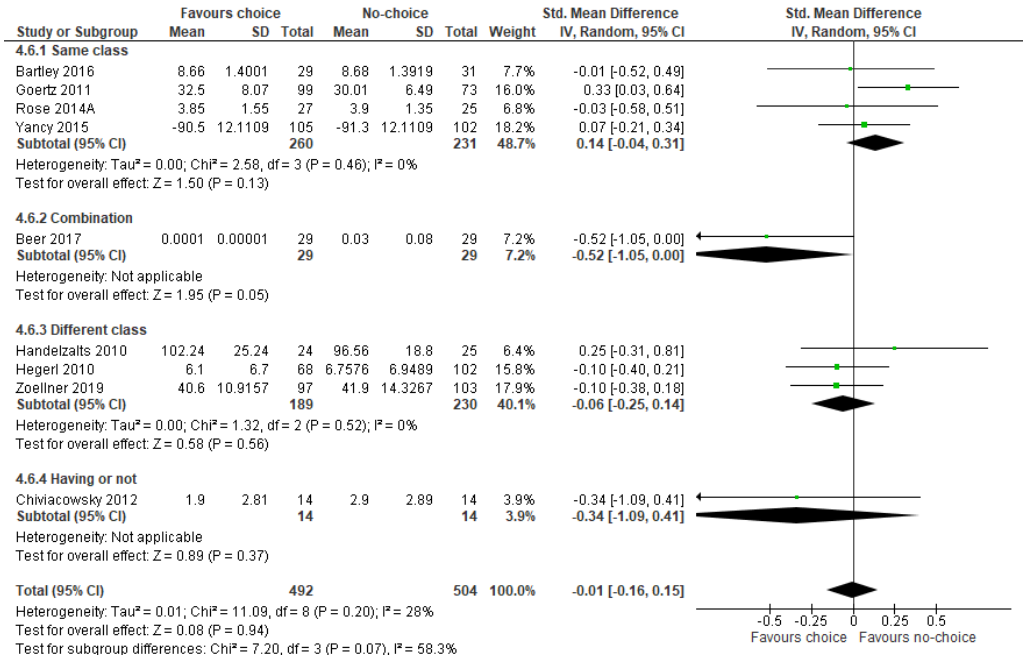


Figure 4.12: Mood according to type of choice



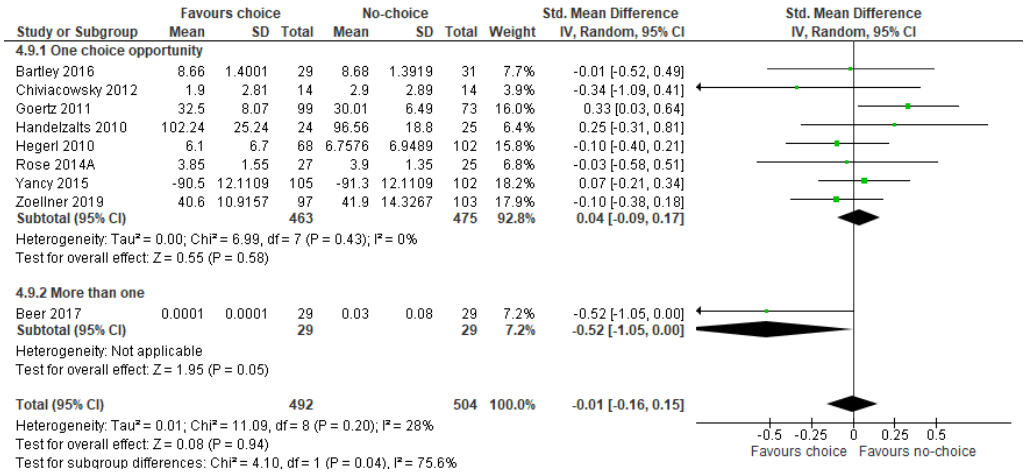
Note: Bartley 2016: short-form State-Trait Anxiety Inventory; Beer 2017: Profile of Mood States – Adolescent Inventory; Chiviacowsky 2012: non-validated questionnaire; Goertz 2011: State-Trait Anxiety Inventory – State; Handelzalts 2010: Sarason's Test Anxiety; Hegerl 2010: Hamilton Depression Rating Scale; Rose 2014A: aggregated likert scales for irritated, uncomfortable and unpleasant; Yancy 2015: Impact of Weight on Quality of Life-Lite questionnaire – distress subscale; Zoellner 2019: Spielberger State-Trait Anxiety Inventory

Features of choice-based interventions: Number of choice opportunities

Two studies offered more than one choice opportunity. One of these reported mood and satisfaction, and the other reported satisfaction only.

Figure 4.13 shows that for the mood outcome, the more than one choice category had a greater effect size than the one choice opportunity groups, favouring choice, however this was not statistically significant (SMD -0.52, 95% CI -1.05-0.00, p = .05). Further, this was again based on a single study where a SD of zero was reported in the choice arm.

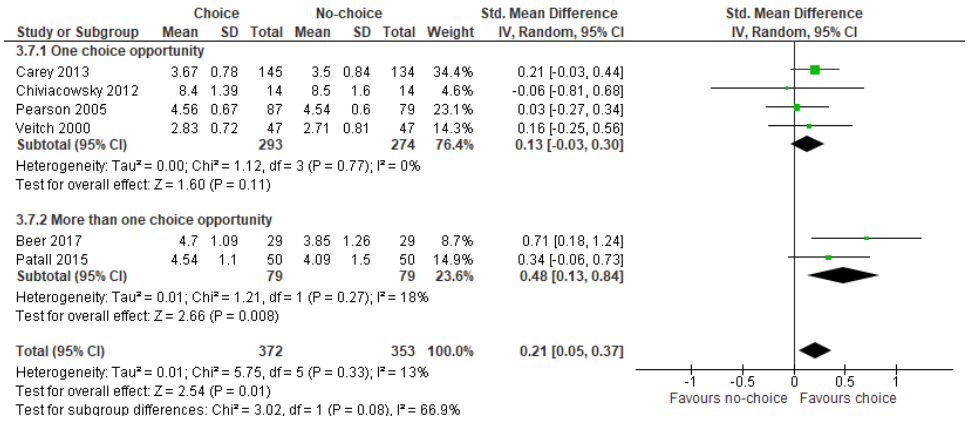
Figure 4.13: Mood according to the number of choice opportunities



Note: Bartley 2016: short-form State-Trait Anxiety Inventory; Beer 2017: Profile of Mood States – Adolescent Inventory; Chiviacowsky 2012: non-validated questionnaire; Goertz 2011: State-Trait Anxiety Inventory – State; Handelzalts 2010: Sarason's Test Anxiety; Hegerl 2010: Hamilton Depression Rating Scale; Rose 2014A: aggregated likert scales for irritated, uncomfortable and unpleasant; Yancy 2015: Impact of Weight on Quality of Life-Lite questionnaire – distress subscale; Zoellner 2019: Spielberger State-Trait Anxiety Inventory

In terms of satisfaction, analyses found that the more than one choice opportunity group resulted in a greater effect size for satisfaction, significantly favouring choice (Figure 4.14; SMD 0.48, 95% CI 0.13-0.84, p = .008).

Figure 4.14: Satisfaction according to the number of choice opportunities



Features of choice-based interventions: Number of choice options

Differences in the number of choice options per choice opportunity were also assessed. Of the 16 studies reporting drop-out, seven provided two choice options, and nine provided more than two. The analyses (Figure 4.15) showed the largest effect size favouring choice was for studies offering more than two options (RR 0.67, 95% CI 0.44-1.04, p = 0.008), although pooled point estimates in the two subgroups were similar. In terms of adherence and satisfaction, larger effect sizes were seen for studies offering more than two choice options, both favouring choice (Figure 4.16, RR 1.25, 95%CI 0.82-1.92, p = .30; Figure 4.17, RR 0.36, 95% 0.07-0.65, p = .01).

Of the nine studies reporting a mood outcome, seven provided two choice options, and two provided more than two (Figure 4.18). The studies providing more than two options showed the largest effect size, favouring choice (SMD = -0.7, 95% CI -0.90-0.77, p = .88). The studies offering two choices favoured choice, however this also was not statistically significant. A sensitivity analysis was conducted for the 'more than two options' category, as one of the two studies reported a mean and SD of zero in the choice group. This analysis

showed that without this study, the SMD increased to 0.33 (95% CI 0.03-0.64, p = .03; Appendix D), changing from favouring choice interventions to significantly favouring no-choice.

Figure 4.15: Drop-out according to the number of choice options

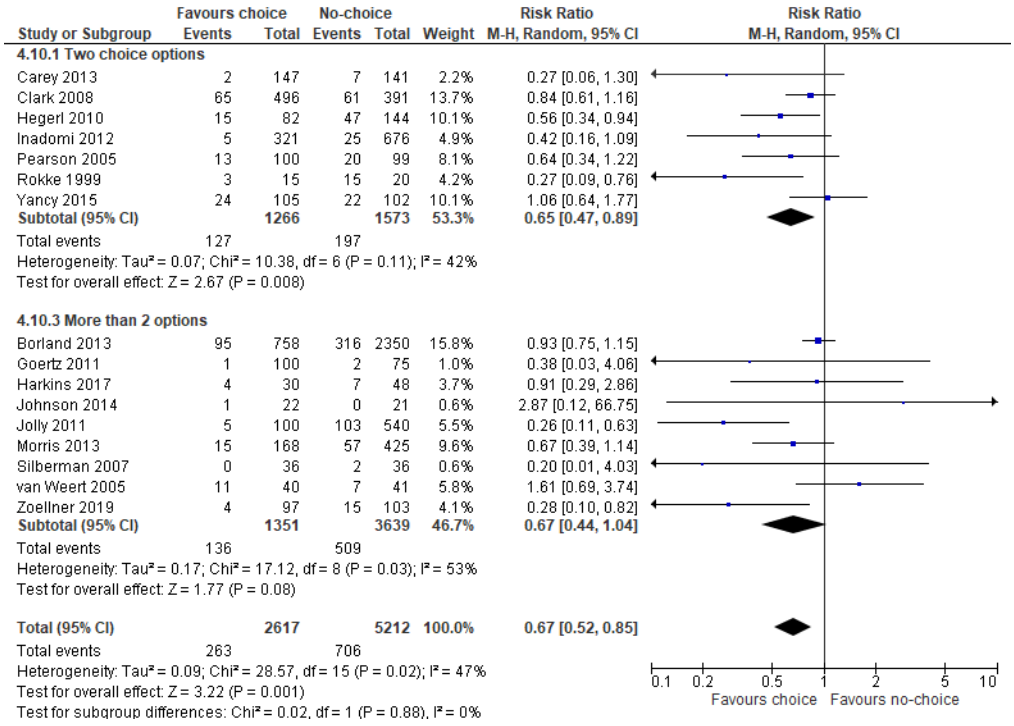


Figure 4.16: Adherence according to the number of choice options

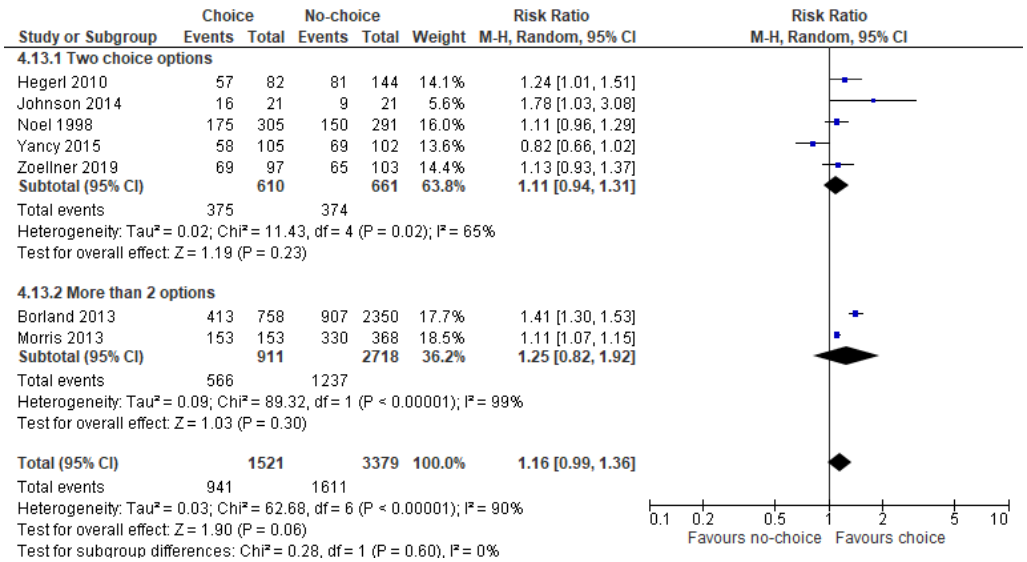


Figure 4.17: Satisfaction according to the number of choice options

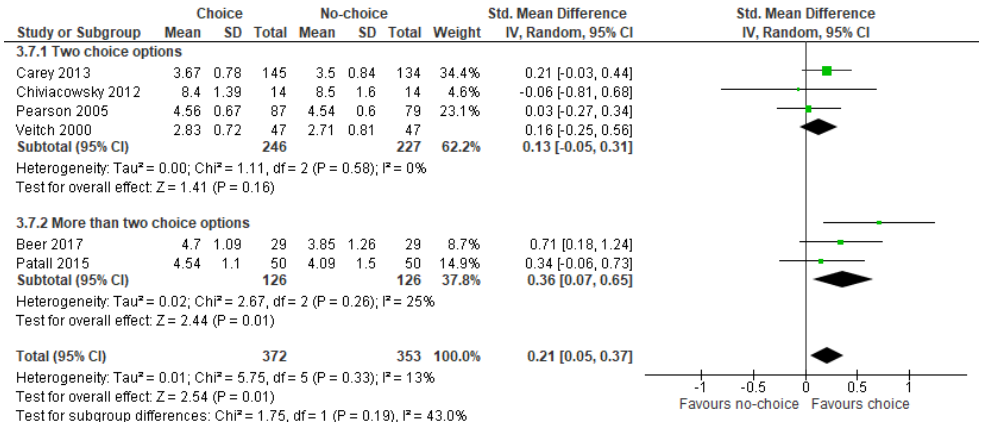
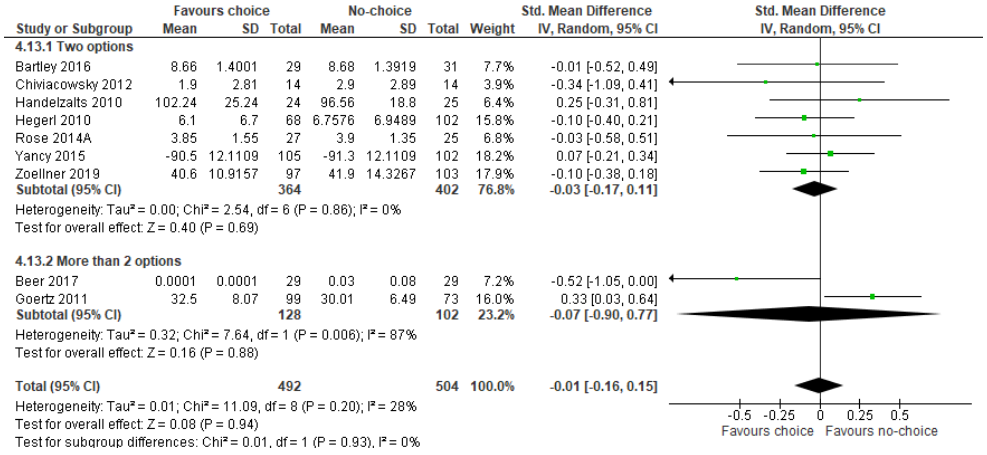


Figure 4.18: Mood according to the number of choice options



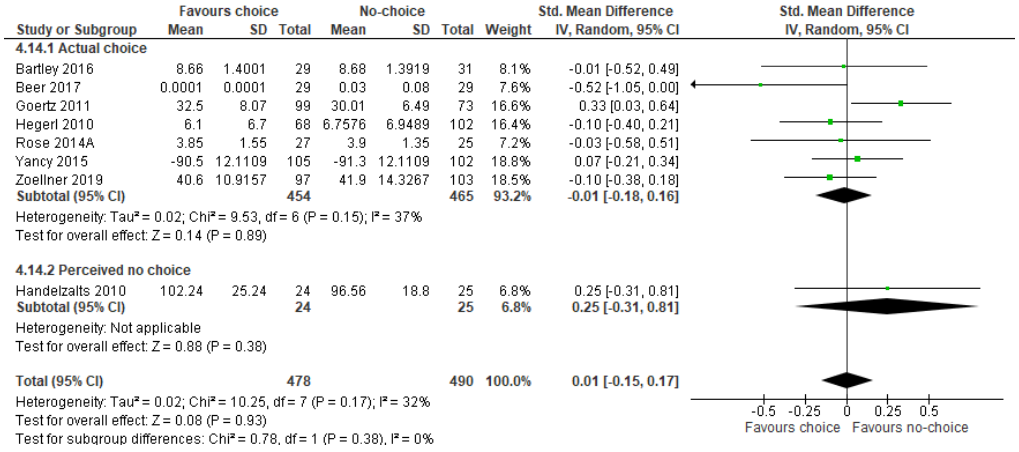
Note: Bartley 2016: short-form State-Trait Anxiety Inventory; Beer 2017: Profile of Mood States – Adolescent Inventory; Chiviacowsky 2012: non-validated questionnaire; Goertz 2011: State-Trait Anxiety Inventory – State; Handelzalts 2010: Sarason's Test Anxiety; Hegerl 2010: Hamilton Depression Rating Scale; Rose 2014A: aggregated likert scales for irritated, uncomfortable and unpleasant; Yancy 2015: Impact of Weight on Quality of Life-Lite questionnaire – distress subscale; Zoellner 2019: Spielberger State-Trait Anxiety Inventory

Features of choice-based interventions: Actual versus perceived choice

The final exploratory analysis compared studies using actual choice to those using perceived choice or no-choice groups. One study used a perceived no-choice control group, and reported a mood outcome. Analysis showed that this study favoured the no-choice group, with a larger effect size than the studies of actual choice showing no difference between groups (Figure 4.19; SMD = 0.25; SMD = -0.01), however neither effect was statistically significant (p = .38; p= .89). A sensitivity analysis was conducted, removing Beer et al.,

(2017) due to reporting an SD of zero, in which the SMD increased to 0.04 (95% CI -0.11-0.08, p = .62).

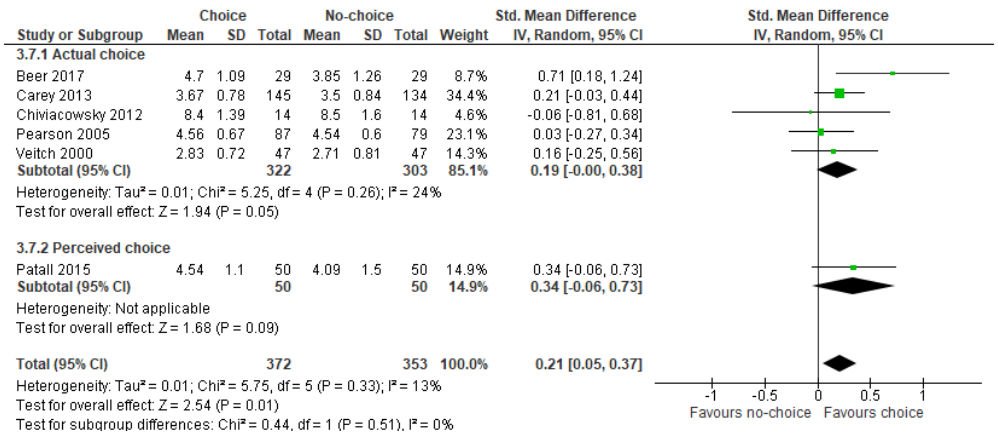
Figure 4.19: Mood according to actual or perceived choice



Note: Bartley 2016: short-form State-Trait Anxiety Inventory; Beer 2017: Profile of Mood States – Adolescent Inventory; Chiviacowsky 2012: non-validated questionnaire; Goertz 2011: State-Trait Anxiety Inventory – State; Handelzalts 2010: Sarason's Test Anxiety; Hegerl 2010: Hamilton Depression Rating Scale; Rose 2014A: aggregated likert scales for irritated, uncomfortable and unpleasant; Yancy 2015: Impact of Weight on Quality of Life-Lite questionnaire – distress subscale; Zoellner 2019: Spielberger State-Trait Anxiety Inventory

Additionally, one study used a mix of perceived and actual choice. In terms of satisfaction, this led to a larger effect size favouring perceived choice (Figure 4.20; SMD 0.34, 95% CI -0.06-0.73, p = .09).

Figure 4.20: Satisfaction according to actual or perceived choice



4.7.4 *Risk of bias*

Risk of bias was assessed per outcome rather than for the overall study. This was to allow for aspects such as the amount of missing data, the method of measurement, and the definition of each specific outcome to be considered. Risk of bias judgements are presented here for outcomes included in the main meta-analyses: drop-out, adherence, satisfaction and pooled negative mood. The quality of these studies varied, however all but two outcomes were given an overall rating of either some concerns (n=23 outcomes) or high risk (n=14 outcomes). Figure 4.21 shows the risk of bias judgements for each item as a percentage across studies. The risk of bias judgements per domain for all meta-analysed outcomes, and those that could not be meta-analysed are included in Appendix E.

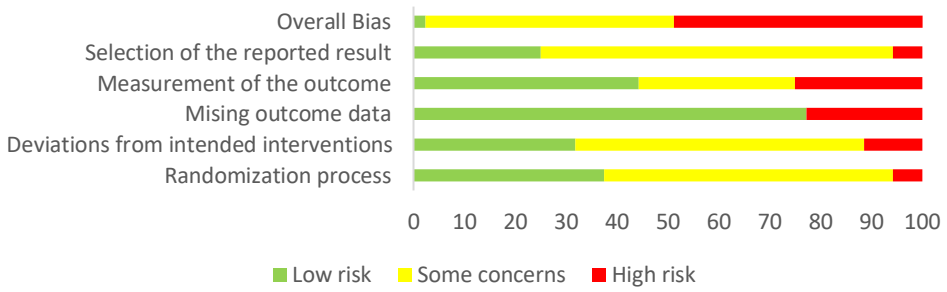


Figure 4.21: Risk of bias items

4.8 Discussion

4.8.1 *Overview of results*

The primary aim of this review was to assess the impact of choice-based interventions on mood-related outcomes. Secondary aims included assessing the impact of these interventions on retention-related outcomes, including drop-out, adherence, and participant satisfaction, and describing the features

of choice-based interventions in order to understand how researchers are currently manipulating and operationalising choice.

4.8.1.1 Effects of choice on mood and retention

In terms of the first two objectives of the review, the results of the meta-analyses were mixed and sometimes limited by small numbers of studies. Retention was assessed on two main levels, including drop-out (i.e. how many people were lost to follow up) and adherence (i.e. how many people adhered to study protocol). Satisfaction was also assessed as a participant reported measure of engagement. Results from the retention analysis suggest that choice can have a positive effect on outcomes such as drop-out and satisfaction, with statistically significant effects favouring choice. Further, the analysis showed some potential positive effects on adherence to the intervention, with the pooled point estimate favouring choice, however this was not statistically significant. Results for the aggregate negative mood outcome suggests that choice-based interventions do not significantly differ from no-choice interventions, with the pooled point estimate marginally favouring choice. It is unclear however, whether this is because the provision choice makes no meaningful difference in terms of mood outcomes, or whether this is a factor of sparse and divergent data making significant findings unlikely. Thus, this suggests that choice is beneficial in terms of participant retention and enjoyment, however the effects of choice on mood are more limited.

It is interesting to note that whilst choice-based interventions improved participant retention and resulted in more adherent participants compared to

the no-choice groups, this did not always translate to better mood outcomes. Of the nine meta-analysed studies reporting a mood outcome, four also reported drop-out. Of these, three reported less drop-out in the choice-based group, however of these three only two showed that this resulted in better mood for those in the choice group. This suggests, contrary to what might be expected, that better participant retention does not necessarily lead to better outcomes. In fact, other research has similarly found that participant attrition may not impact study outcomes, including palliative treatment outcomes (Strömgren et al., 2005) and behaviour change outcomes such as the number of alcoholic drinks consumed (Kypri, Bowe, Karlsson, & McCambridge, 2020). One potential explanation of this is that those who drop out may represent a population with more severe symptomology, poorer health, or who are less engaged, making them less able or likely to achieve a good intervention outcome. Alternatively, drop-out may in fact be a consequence of early treatment success to the point where participants no longer need to continue with treatment, or effective interventions whereby participants gain sufficient benefit even with early discontinuation.

Adherence, on the other hand, has been associated with better outcomes in a number of studies, showing that increased adherence is related to greater decreases in depressive symptoms (Fuhr et al., 2018; Sirey, Bruce, & Kales, 2010) and improvements in anxiety (Arndt, Rubel, Berger, & Lutz, 2020), as well as outcomes such as greater reductions in disability and pain (Friedrich, Gittler, Halberstadt, Cermak, & Heiller, 1998). When comparing mood-related outcomes with adherence to intervention outcomes in this review however, conclusions are limited by the modest number of contributing studies. Only three studies reported both adherence and mood. Of these, two showed that

those in the choice arm were more adherent to the intervention, and also had better mood outcomes. The other showed that those in the no-choice group were more adherent to the intervention, and favoured the no-choice group in terms of the mood outcome. Further studies of choice compared to no-choice interventions including both adherence related outcomes and mood are needed to address this, and determine whether choice may be a mechanism through which adherence leads to greater mood change.

Anticipated absolute effects

This review also considered the minimally important differences (MIDs) in the effects of choice-based interventions, based on absolute effects. For many outcomes, there is no definitive agreed upon method of assessing MIDs, which represent the practical, rather than statistical, importance of a treatment effect, as they are highly dependent on the context, and thus this assessment can be subject to a degree of subjectivity. In terms of the main outcomes of this review, the anticipated absolute effects for retention-related outcomes demonstrated that there were 48 fewer dropouts per 1000 participants, 90 more adherent participants per 1000, and an increase of 0.21 standard deviations in satisfaction in choice-based groups. This is equivalent to a 5-9% improvement in the dichotomous outcomes, which may be considered as meeting the threshold for a MID in some contexts (e.g., National Institute for Health and Care Excellence, 2019). In terms of the negative mood outcome, there was an increase of 0.04 standard deviations compared to the no-choice group, indicating that as well as not being statistically significant, this difference also probably did not meet the threshold indicating an important difference, given that some consider a change of 0.5

standard deviations a benchmark for important differences (Norman, Sloan, & Wyrwich, 2003).

4.8.1.2 The features of choice-based interventions

In terms of the final objective, assessment of the included studies revealed that they varied significantly in terms of the interventions used, the type of participants, the specific outcomes that were assessed, and the methods of assessing them, as well as the choice manipulation itself and the various parameters regarding choice. The following sections discuss the results of the meta-analysis in terms of the various ways in which choice was operationalised, including the type of choice, number of choices and options for participants to select, and whether the choice was real or perceived.

Type of choice

One area worthy of comment is what the results of the analyses tell us about how the type of choice influences the effects of choice on outcomes. In their review of the effect of choice on motivation, Patall et al., (2008) defined five categories of choice intervention, and found significant differences between choice types in terms of their effect on motivation, with the largest effects seen for 'instructionally irrelevant' choices (i.e., choices that could not change the effectiveness of the task). In the present review, six categories were defined as a result of an iterative process of comparing and contrasting the studies included. Of the 32 included studies, 20 fell under the category 'same classification of intervention', with the studies comparing two or more different versions or formats of a specific intervention. Unlike Patall et al., (2008), the results of this meta-analysis suggest that overall, the different types of choice are not significantly different from each other in terms of their effects on the

included outcomes. For all outcomes there was either no significant heterogeneity, or heterogeneity was not explained by subgroup analysis, despite including studies employing a variety of different choice types. This suggests that the different types of choice interventions either did not differ in their effects, or that differences were not caused by the type of choice. In terms of both drop-out and adherence, the largest effect size was seen for 'different class' interventions (i.e., those with two or more distinct interventions), whereas for both satisfaction and mood, 'combination' interventions (i.e., interventions with a combination of the other choice types) had the largest effect, with all effects favouring choice.

Overall, given the lack of heterogeneity, the results from this review suggests that whilst choice interventions are more effective than no-choice interventions for some outcomes (namely retention-related outcomes), the way in which the choice is given, in terms of type of choice, does not matter.

Number of choices

The number of choices in a study can refer to both the number of choice opportunities (i.e., the number of times a participant can make a choice), or the number of choice options per choice opportunity (i.e., the number of options to pick from when making a choice). For instance, in a task a participant may be able to choose whether to do the task in the morning or afternoon, and which one of three maths problems to solve. In this example, the number of choice opportunities is two, with two choice options in the first opportunity and three in the second. In terms of the former, Patall et al., (2008) found that the largest effects were seen when between three and five

options were available. In the present review, only three of the 32 studies involved making more than one choice, and only two of these could be included in the meta-analyses. One involved participants making five different choices, and in the other, participants made three choices. Results of the meta-analyses showed that these studies had larger effect sizes favouring choice for the outcomes they reported (satisfaction and mood), compared to those with only one choice opportunity. Consistent with Patall et al., (2008), this suggests that making multiple different choices may be more effective across outcomes, compared to making a single choice. This may be due to the increased number of choices resulting in an increased sense of autonomy, consistent with self-determination theory (Deci & Ryan, 1980). However, it is important to note that given that this is based on just two small studies, certainty surrounding this finding is low.

In terms of the number of options to choose from, only 13 of 32 studies provided participants in the choice group with more than two options to choose between. Exploratory subgroup analyses showed that for negative mood, the biggest effects were seen for studies with more than two choice options, whereas for drop-out, the largest effect sizes were seen for studies with two choice options. However, for both outcomes differences were minimal.

Overall, analyses for all outcomes showed either no heterogeneity, or that the heterogeneity that was present was not explained by subgroup analyses according to the number of choices opportunities or options, suggesting that the included studies' results did not differ significantly from each other based

on this factor. Whilst this goes against previous findings relating to intrinsic motivation specifically, this inconsistency might be explained by the differences not being large enough to cause significant heterogeneity. Alternatively, the difference in results between Patall et al.,'s review on motivation and the current review may be that the number of options is more important for outcomes relating to motivation, rather than mood or retention-related outcomes. Overall, the analyses in the present review suggest that the number of options provided per choice opportunity does not significantly impact the effect of the choice intervention on drop-out or mood, and that restricting choice to only two options does not necessarily have an adverse effect caused by a sense of choice restriction.

Perceived or actual choice

Finally, the impact of actual versus real choice should be considered. In the present review, one study employed a perceived no-choice group, where participants were led to believe they would be randomised when in fact they were assigned according to their preference. Interestingly, out of the four studies reporting anxiety, this study showed the greatest standardised mean difference between the two intervention groups, suggesting that perception of choice or no-choice may in fact be more important than the actual provision or denial of choice. However, the direction of this effect was favouring the perceived no-choice group, indicating that this group had lower anxiety levels than choice group participants, despite the choice group having significantly higher levels of perceived control. This finding goes against the self-determination theory, which would expect that those with greater perceived control, achieved through the provision of choice, would have more beneficial outcomes. It is however worth noting that this single study was small, with 24

and 25 participants per arm and therefore may not have been adequately powered to detect statistically significant differences.

The other study involved perceived choice, where participants in the choice group believed they were choosing the task difficulty, when in fact all choice and no-choice group participants received the same task difficulty. Whilst this study showed that those in the choice group had both higher perceived choice scores and greater satisfaction scores than those in the no-choice group, supporting the self-determination theory, the study involved other additional choices that were real, and so conclusions regarding the role of perceived as compared to actual choice cannot be made.

4.8.2 *Other considerations*

Study design

Studies were categorised into three types of study design: traditional RCT, two-step RCT, or matched designs. Twenty-four of the 32 studies used a traditional or two-step RCT approach, whilst only eight used matched designs. The meta-analyses indicated that for all but one outcome there was no serious heterogeneity. For the adherence to the intervention outcome, there was significant heterogeneity, which was not explained by subgroup analysis according to study design, indicating that the type of study design did not cause variation in the effect of choice compared to no-choice. However, all studies included in this analysis were either traditional or two-step RCTs, therefore it would not necessarily be expected for there to be differences in outcomes relating to the study design. On the other hand, matched designs may result in a greater sense of restricted choice for control group participants

than randomised designed, provided participants are aware that another participant is, in essence, making the choice for them. This may result in a greater difference between groups, caused by an increased sense of control and autonomy in the choice group, and an increased sense of restriction and lack of control in the no-choice group. Indeed, whilst other analyses did not show serious heterogeneity, analyses showed that studies with matched designs had larger effects compared to both traditional and two-step RCTs for all other outcomes.

Age

Given the focus of this thesis on older adults, a sensitivity analysis was undertaken for the six studies that included this age group. Analysis for the most commonly reported outcome by these studies showed that drop-out was not significantly different between studies with an older adult population compared to younger adults or children. Effect sizes were also similar in the two groups, suggesting that the effect of choice on this outcome was not moderated by age. This suggests that the mechanism through which choice exerts positive effects on drop-out, and potentially mood, whether it is the increase in control, relevance or autonomy, does not differ across age groups, and that choice is valued at all ages.

4.8.3 ***Limitations and difficulties***

Several difficulties were encountered when carrying out this review and meta-analyses. Choice-based interventions are poorly defined, and often described using other terms such as individualisation, preference and participant-selected. Thus, when conducting the systematic review search, terms had to

be kept broad, so as to not miss relevant studies that were not obviously described as being choice-based. This led to a very large number of potentially relevant references being identified for potential inclusion.

The studies that were included were very heterogeneous in terms of the specific intervention, population, and outcomes used. Traditionally, such diverse studies would not be meta-analysed together, however as one of the aims of this review was to explore the effect of choice on the selected outcomes, regardless of the specific intervention and population, to see whether there was an overall effect of choice, this method was judged to be appropriate. Further, exploratory subgroup analysis based on the differing features of the included studies was able to indicate whether these differences were the cause of the heterogeneity. The strict nature of the study inclusion criteria, designed as such in order to increase confidence in any observed differences between groups being due to choice alone and not other factors, such as interventions that were only available to one group, had an additional advantage of minimising the heterogeneity of included studies as much as possible. For instance, the criteria that study arms could only differ in the provision of choice meant that studies where choice groups were given more options than that assigned to no-choice groups, or conversely studies where no-choice groups were assigned to interventions that were not included as a choice available to choice group participants, were excluded. This meant that included interventions were as comparable as possible. However, it does limit this review to make judgements on only the specific type of study design that was included, whilst a number of alternative designs have been and are being used.

Finally, all but two of the included outcomes were judged as having some concerns regarding risk of bias, or high risk of bias, therefore reducing confidence and adding a degree of uncertainty to the results of the analyses. One of the main challenges for this type of study in regards to the risk of bias is the fact that participant blinding is not possible for participants, coupled with the fact that many outcomes are self-reported by participants, leading to potential bias due to expectations surrounding the provision of choice. Further, participants may be more likely to rate an intervention more favourably if they have had an active role in determining the specific content of their intervention, compared to being assigned an intervention. This may be because having an active role in their intervention content may not only increase autonomy, but also lead to a sense of responsibility and accountability, increasing the likelihood of positive appraisals. Thus, it is possible that by their very nature, choice-based interventions introduce bias in this way.

4.8.4 *Implications*

One of the aims of this review was to provide an overview of the type of choice-based interventions currently being carried out by researchers in a number of areas. Thus, this review addresses a gap in the current literature, by being the first to bring together the existing evidence for this type of intervention, in terms of retention and mood-related outcomes. This will allow researchers seeking to conduct research in this area to understand what has and has not been done, to allow for an informed choice regarding intervention design, and to identify the designs used in their own field to enable more comparable studies to be carried out, allowing for greater confidence in future reviews. Thus, based on the results of this meta-analysis, researchers may

want to consider the inclusion of a choice-based intervention arm, particularly if there are concerns regarding participant retention, adherence or satisfaction. Whilst participant satisfaction may not be a key outcome in many research projects, researchers should strive for providing participants with the best experience possible whilst taking part, not only to improve the research experience for the participant, but also to improve research engagement and foster good relationships between the research and public communities. Further, evidence has shown that participant satisfaction is related to better outcomes in a number of research contexts, including reduced alcohol intake (Fodor, Grekin, Beatty, McGoron, & Ondersma, 2020; Kendra, Weingardt, Cucciare, & Timko, 2015), functional outcomes following surgery (Soroceanu, Ching, Abdu, & McGuire, 2012), weight loss (Shapiro et al., 2012), and clinical outcomes such as postprandial glucose levels in individuals with diabetes (Peyrot & Rubin, 2009). Thus, the provision of choice may not only enhance satisfaction, but also impact on some research outcomes. Researchers should consider the type of choice as well as number of choices and options, although this review suggests that there may not be significant differences between these different choice parameters.

This review has also identified areas where evidence is lacking, and further research is required. For instance, it remains unclear whether there are differences in the effectiveness of choice-based interventions between genders, ages and cultures. The heterogeneity between different study designs has also resulted in a very small number of studies specifically investigating comparable populations and specific outcomes, making comparisons difficult and based on a small number of studies, indicating a general need for more research in this area to build up the evidence base.

Finally, this review has highlighted the lack of high-quality studies with sufficiently powered sample sizes. Future work should look to address this by carrying out appropriate power calculations, and minimising potential bias where possible by adhering to practices such as publication of study protocol and clear and transparent reporting in study papers.

For researchers in general, this review highlights that whilst the provision of choice may not necessarily lead to better outcomes, with mixed findings mood-related outcomes, it is clear that choice will lead to better participant retention and satisfaction. Thus, researchers should consider the provision of choice when designing mood-based interventions to minimise participant drop-out and missing data. This may also translate to clinical as well as academic settings, where the provision of choice to patients wishing to make health related lifestyle changes or suffering from negative mood, may result in reduced discontinuation and greater satisfaction in their treatment.

In the context of this thesis, there was particular interest in the effect of choice on positive mood. However, only two studies included measures of positive mood, including pleasure and happiness. In separate analyses, both studies showed that choice-based interventions may lead to greater improvements in these positive mood outcomes, although the differences between groups were not significant. However, both studies had very small sample sizes, thus it is possible that they were not sufficiently powered to detect significant changes between groups. Therefore, larger studies powered to detect changes in positive mood outcomes may show a significant effect of choice compared to no-choice. Further, there were significant differences between intervention

groups, favouring choice in terms of satisfaction in an analysis including six studies and just over 700 participants. There is potentially some overlap between satisfaction and positive mood, thus this further suggests that in an appropriately powered study, the effect of choice of choice on positive mood may be significant, as observed for satisfaction and/or enjoyment. Overall, whilst this evidence is certainly not convincing, there is potential, which warrants further investigation.

4.9 Chapter summary

This review demonstrated that the choice-based interventions currently being carried out by researchers vary greatly in terms of participants, settings, and several factors relating to the provision of choice itself. However, despite this variation, there is good evidence that choice-based interventions are feasible. They lead to a reduction in participant drop-out and are liked by participants more than no-choice interventions. Whilst there remains some uncertainty with regard to whether choice-based interventions are more effective than no-choice interventions in terms of mood outcomes, there are reasons to believe that the provision of choice may be beneficial in this context. However, more evidence is needed. Therefore, the next chapter aims to contribute to this literature though the development of a choice-based mood intervention for use in a mood induction study to enhance antibody responses in older adults receiving the influenza vaccination. The chapter will also describe the methodology for a randomised controlled clinical trial utilising this choice-based intervention, to assess whether choice-based interventions are more effective than no-choice interventions in enhancing mood, and whether this results in greater antibody responses to vaccination.

5 Chapter 5: Enhancing Influenza vaccination by optimising mood in older adults: design and methods of the Flu and Mood in older adults (For-ME) randomised controlled clinical trial

5.1 Chapter overview

As outlined in Chapter 3, a feasibility study has previously demonstrated that a positive mood intervention is effective at enhancing mood on the day of vaccination, and may lead to increases in antibody response. It is currently unclear whether this intervention could be improved, how it compares to usual care alone, and whether these results can be replicated. The results of the systematic review detailed in Chapter 4 suggests that choice-based interventions may have advantages compared to no-choice interventions, with strong evidence suggesting benefits for participant retention and satisfaction, some potential benefits in terms of adherence, and inconclusive evidence regarding mood. Thus, this chapter sets out to outline the development of a larger scale, three-armed randomised controlled trial, comparing the positive mood intervention used in the previous feasibility study, with a newly developed choice-based positive mood intervention, and a usual care control condition. By comparing these three arms in terms of both mood and vaccine response outcomes, this trial will address the questions previously raised. This chapter will firstly describe the initial considerations for both the choice-based intervention development and study design, including how the intervention might work, the vaccination choice, study length, measurement of affect, and treatment of the control group. The second part of this chapter will describe the final design used based upon these considerations.

5.2 Background

Ayling et al., (2018) demonstrated that a brief positive mood intervention shortly before influenza vaccination was able to significantly increase positive mood, however, as stated above, several questions remain unclear. This chapter describes a randomised controlled clinical trial to address these remaining questions. The overall goal of this trial is to act as a definitive trial of the interventions' impacts on mood, whilst also exploring effects on immunological outcomes. This may go on to inform a future trial, on a much larger scale and sufficiently powered to detect significant changes in antibodies and/or clinical outcomes.

5.3 How the intervention might work

Chapter 3 outlined evidence demonstrating that positive affect can impact the immune system, however the mechanisms through which this effect occurs remains unclear. Whilst two models outlining the relationship between stress, immunity and health were described in Chapter 2, here two additional but similar models are detailed directly relating to positive affect (PA), including the main effect model, and the stress-buffering model.

5.3.1 *The main (direct) effect model*

The main effect model (Pressman & Cohen, 2005) of positive affect and heath posits that PA influences health outcomes via four key mediators: health practices, social ties, and physiological processes such as ANS and HPA axis activity, and endogenous opioids. Health practices may be directly influenced by PA, in particular high activation PA, by increasing positive health behaviours such as more exercise, better diet, better sleep quality and

increased adherence to medications (Cohen et al., 2003; Hoogwegt et al., 2013; Ironson, Kremer, & Lucette, 2018; Kelsey et al., 2006; Ong, Kim, Young, & Steptoe, 2017; Ryff et al., 2004; Whitehead, 2017), all of which may lead to better health outcomes. Studies of PA manipulation have found that increasing PA can lead to increased intentions to eat healthy food and engage in physical activity (Cameron, Bertenshaw, & Sheeran, 2015, 2018). However, other studies failed to find benefits of induced PA in terms of physical activity in people with coronary artery disease, and medication adherence in people with hypertension (Ogedegbe et al., 2012; Peterson et al., 2012).

Social factors such as social support have also been linked with both PA and health outcomes. For instance, those with higher PA report more and better quality social ties (e.g. Berry, Willingham, & Thayer, 2000; Diener & Seligman, 2002). Increased social support may then influence both health practices, as well as impacting on the ANS and HPA axis, both of which may influence health outcomes. As well as social support, PA is predictive of accrual of a range of other resources, including both coping and physical resources such as financial success (De Neve & Oswald, 2012; Gloria & Steinhardt, 2016).

PA may also influence health through physiological functioning. For instance, PA is associated with a range of physiological systems, including immune function, cardiovascular function and the stress response. Trait PA is associated with lower levels of adrenaline and noradrenaline, although high arousal PA may be associated with increases (Pressman & Cohen, 2005). Cortisol may also be reduced in those with increased PA, both state and trait (Brummett, Boyle, Kuhn, Siegler, & Williams, 2009; Steptoe, Wardle, &

Marmot, 2005). Reductions in these hormones may lead to reductions in the negative impacts of activation of the stress response on health. PA has also been linked to lower heart rate and blood pressure (Blanchflower & Oswald, 2008; Steptoe et al., 2005), as well as increased endogenous opioids. Endogenous opioids may influence health via the ANS and HPA axis, by reducing autonomic and endocrine activity (Drolet et al., 2001), therefore high PA may lead to a reduced stress response via the opioid system.

Thus, according to this model of PA, whilst more stable trait-like PA is likely to impact immune functioning through several mechanisms, state PA may exert effects on the immune system though physiological mechanisms such as cortisol and endogenous hormone levels. Therefore, it is through these latter mechanisms by which a brief positive mood intervention may enhance immune responses to vaccination.

5.3.2 *The stress-buffering model*

A second, complementary model suggests that PA may be able to act as a buffer for the negative impact of stress on the body (Pressman & Cohen, 2005). PA may do this through a number of mechanisms. Firstly, PA may lead to positive, restorative health practices, such as sleep, exercise and relaxation (Smith & Baum, 2003). Secondly, PA may trigger the release of endogenous opioids which act to diminish the ANS and HPA pathway responses, and therefore reduce the negative impact of stress on the immune and cardiovascular systems (Smith & Baum, 2003). PA may directly lead to a reduction in the experience of stress, due to those high in PA being less likely to encounter stressful situations, such as social conflict (Pressman & Cohen,

2005; Uchino, Smith, Holt-Lunstead, Campo, & Reblin, 2007). As well as reducing overall exposure to stress, thus resulting in better physiological functioning, this may also lead to more desirable health behaviours such as healthy eating. PA is also associated with increased resources, including social, physical, and psychological resources (Ashby & Isen, 1999; Fredrickson, 1998; Salovey, Rothman, Detweiler, & Steward, 2000). For instance, physical and social resources may be increased due to more exploration and creativity, whereas psychological resources may be enhanced by the promotion of resilience and optimism. Although PA may be short-lived, these resources gained as a result will be long-lasting. The presence of these increased resources may influence how we appraise a stressful situation thus reducing the stress response or may impact health practices and promote healthier behaviour. Finally, PA may influence the recovery from the stress response. For instance, experiencing PA after experiencing a stressor may lead to a faster return to baseline cardiovascular reactivity (Fredrickson, 1998; Fredrickson, Mancuso, Branigan, & Tugade, 2000). Given that both increased reactivity and prolonged recovery are associated with detrimental long-term health effects (Fredrikson & Matthews, 1990), faster recovery caused by PA may negate this danger.

According to this model, PA may act as either a moderator, or a mediator (Pressman et al., 2019). For instance, PA may moderate the relationship between stress, health behaviours, and physiological functioning, where the higher the level of stress, the more protective PA is. Alternatively, PA may mediate the relationship, by influencing the experience of stress through the reduction in stressful situations or faster recovery from stress, resulting in improved health outcomes.

Thus, according to this model, a brief mood enhancing intervention may lead to enhanced immune responses by reducing the impact of stress. Therefore, it may be expected that the greatest benefits of mood enhancement may be seen in those with greater stress levels.

5.4 Initial considerations

5.4.1 *Vaccination choice*

The type of influenza vaccine to be included in this study was a key consideration. Three different influenza vaccines were identified as being equally effective and available for use in adults over 64 years in the UK for the 2019-2020 flu season, including an adjuvanted trivalent vaccine (aTIV) similar to the only one recommended the previous year, and two newly licenced vaccines: one a cell based quadrivalent vaccine (QIVc), and the other a high dose trivalent influenza vaccine (TIV-HD) (Joint Committee on Vaccination and Immunisation, 2018; NHS, 2019). As each vaccine is slightly different in terms of either the number of vaccine strains or the dose of the vaccine, it was important to limit those in the study to just one type of vaccine, to reduce potential variability that may be introduced by using different vaccine types. Given the significantly higher price of the TIV-HD vaccine, this type was not eligible for reimbursement under the NHS influenza vaccination programme, and thus was unlikely to be used by GP practices. Of the two remaining vaccines, it became clear after communication with several GP practices that the aTIV was going to be most commonly used vaccine for the 2019/2020 influenza season and so was chosen for this trial.

5.4.2 *Study length*

Another key consideration was determining the duration of the follow-up period. The previous feasibility study included blood samples taken at both four- and 16-weeks post-vaccination. Given that previous research has indicated that peak IgG antibody levels occur at approximately four weeks post-vaccination (Gross et al., 1996), this time-point was considered most critical. Whilst a second follow-up blood sample at 16-week post-vaccination would provide valuable information regarding the long-term vaccine response, as well as allowing follow-up during the time period when influenza viruses are most frequently circulating in the UK (Public Health England, 2019d, 2020), there were two key pragmatic reasons for not including this longer-term follow-up point. Firstly, a second follow up sample would produce approximately 650 additional samples to be analysed, with both time and financial implications. Secondly, an additional follow-up visit would significantly increase participant burden. Thus, it was decided that only the four-week sample would be collected, meaning that the total time of participant involvement was four weeks.

5.4.3 *Measuring affect*

The majority of studies measuring affect use self-report measures, with many studies employing adjective checklists measures such as the Positive and Negative Affect Schedule (PANAS; Watson et al., 1998) or the Profile of Mood States (POMS; McNair et al., 1971). The benefits of these scales are that they are both validated and provide reliable assessments of affect, and both include both positive and negative affect words. However, they are biased towards positive affect, and mainly focus on high activation affects (i.e., states such as excitement or exhilaration). Further, both measures are lengthy (20

and 65 items respectively), and so there was a concern regarding participant burden. Both do have shortened versions (Curran, Andrykowski, & Studts, 1995; Thompson, 2007), however with the POMS-SF including 37 items, it was still considered burdensome. In the previous feasibility study, three measures of mood were included, including the PANAS, the affective slider (Betella & Verschure, 2016), and a pictorial measure developed as part of the study. Feedback from Public and Patient Involvement (PPI) groups (detailed in section 5.5) suggested that the affective slider was well liked, however the PANAS and the pictorial measure were less acceptable, and therefore should be replaced. Although verbal measures of state affect such as adjective lists, are commonly used, previous researchers have outlined benefits of non-verbal measures, including a quicker completion time and accessibility for those with low literacy skills (Lorish & Maisiak, 1986). Therefore, it was important in the present study to include both traditional verbal measures as well as non-verbal assessments of state mood. Other considerations included the ability to assess both positive and negative affect, as well as both high and low activation levels. Further, it was important that the measure was validated whilst also being brief in order to reduce participant burden. Thus, the Scale of Positive and Negative Experience (SPANE; Diener et al., 2010) was identified as fulfilling the aforementioned criteria. Further, the SPANE did not include specific adjectives that had been identified by PPI group members as being confusing or difficult to understand. In terms of a non-verbal measure of mood, several options were identified and considered, including the circumplex affective grid (Russell, Weiss, & Mendelsohn, 1989), Self-Assessment Manikin (SAM; Lang 1980), the Pick-A-Mood (PAM; Desmet et al., 2016), and the Dynamic Visual Analogue Mood Scales (D-VAMS; Barrows, 2016). The affective grid, SAM and PAM were eliminated, due to either concerns regarding the complexity of the measures, or an inability to readily adapt to a

digital format for use on the tablet devices. The D-VAMS was a measure specifically designed for non-verbal assessment of mood, including both high and low valence, and high and low activation, originally aimed at those who had had a stroke. It was also specifically designed for use on a digital platform. Thus, this measure was selected as the non-verbal measure of mood for this trial.

5.4.4 *Type of control condition*

The control condition used in the previous feasibility study was a neutral mood intervention. However, as noted in Chapter 3, there were several issues with this form of comparator, including the fact that it does not allow for assessment of whether the mood enhancing intervention increased positive mood more than usual care. Thus, the decision was made for the control group to be a usual care comparison, however there were several considerations to take into account in terms of the specific treatment of the usual care group. Firstly, usual care in this context can be quite heterogeneous across GP practices, with some asking patients to pre-book appointments, and some holding 'flu clinics', where waiting times can vary dramatically. In the context of the trial, differences between groups in duration or format (i.e. group or individual) may have unintended consequences on intervention outcomes, due to differences in the contact time with researchers or other participants, for instance. Thus, it was important to ensure that the control group was matched in terms of time and attention as much as possible. Based on this, it was decided that the control group should be matched to the duration of the intervention groups (i.e. 15 minutes). Therefore, the control group participants were asked to wait for a period of 15 minutes, either in a study room or GP office, with a researcher on hand in case of any

problems and to direct the participants to receive their vaccination once the wait was over. This procedure was identical to that of the participants in the intervention arms. A second consideration involved potential contamination resulting from control patients being able to observe the intervention when being viewed by intervention participants. To minimise this risk, it was decided that control group sessions should be separate from the two intervention groups. This meant that researcher blinding to the control group would not be possible. However, by the very nature of the usual care group, in which participants would not be watching an intervention, blinding to this group was unlikely to be possible regardless. Finally, there was consideration regarding whether control group participants should complete questionnaires both at the beginning of the 15 minutes and at the end, as with intervention group participants, or as a one-off measure. On the basis of other similar studies of brief mood interventions (e.g. Pawlow & Jones, 2005; Rider et al., 1990), and to reduce as much between group variation as possible, it was decided to have two measurements of state mood, one at baseline, and one following the 15-minute period.

5.5 Public and Patient Involvement

PPI is an important part of healthcare research; recognised as a critical aspect of the research process and is widely considered best practice (Absolom, Holch, Woroncow, Wright, & Velikova, 2015). The aim of PPI is to shift research away from being 'to', 'about' or 'for' patients and those who have experience of a condition, and towards being carried out 'with' or 'by' them (INVOLVE, 2020). Increasingly, the inclusion of PPI is a requirement of many funding bodies as a condition of funding (Patient-Centered Outcomes Research Institute, 2014; Richards, Snow, & Schroter, 2016; van Thiel &

Pieter, 2013). Indeed, the benefits of PPI are plentiful for both the researcher and the PPI group, and include the broadening of a researchers' perspective and sources of influence, the generation of novel ideas and challenges, the reduction of research waste, and increasing the legitimacy of research and decision making, as well as increasing public engagement in research, and improving the patient experience (Chalmers et al., 2014; Chu et al., 2016; Maccarthy, Guerin, Wilson, & Dorris, 2019; Quennell, 2003). Specifically, PPI input can be used in hypotheses generation, improving research design to reduce attrition and increase feasibility, assessing the appropriateness and wording of participant documents, improving the dissemination of findings, and assisting with implementation of the research itself (Brett et al., 2014; British Geriatrics Society, 2018; South et al., 2016).

The PPI group used for this study included 19 older adults aged 65-85 years who had participated in the previous observational or interventional study (Ayling et al., 2018; 2019). There were three meetings in total over a period of seven months, all of which employed a semi-structured focus group design. Attendance at the three meetings ranged from seven to nine members, and all lasted approximately 1.5 hours.

The aims of the meetings included gaining feedback on the trial design and whether the group thought that it was a good idea, to have participant documents checked for understanding, to generate ideas for the choice-based intervention content, to assess each version of the choice-based intervention for usability and technical issues, and to determine what aspects of the previous intervention experience were important to keep for the current

intervention. A summary of the issues raised and changes that were made as a result can be found in Table 5.1.

At the first meeting, feedback regarding the trial concept and design was positive. Participant documents were said to be readable and easy to understand, although there were some comments regarding the length of some of the documents. Thus, it became clear that whilst the group felt it was important to be well informed, it was also important to balance this with keeping documents as brief as possible. The group then tested the first iteration of the newly developed choice-based intervention, based on the previously trialled standard fixed-content intervention, which consisted of various comedy clips, uplifting music, jokes and positive imagery (full description in section 5.6.5). The choice intervention included similar content, but allowed participants to select which specific video clips they wanted to watch. The group also advised on the appropriate number of choice options available for each choice category, after stating that having one option was too limiting. Therefore, this was expanded to three options per category in the next iteration of the choice-based intervention. The group also considered the state mood measures, and felt that both the PANAS and pictorial measure, were unclear and confusing, therefore alternatives were explored. Additionally, some aspects including the affective slider and selection of video clips required clearer instructions.

Table 5.1: Issues raised in PPI meetings and changes that were made in response

Item	Issue raised	Changes made
Meeting 1		
PANAS	Issues understanding some of the items i.e., 'strong'	Measure was replaced with the SPANE
Pictorial measure	High degree of variability in interpretation of pictures	Measure was replaced with the D-VAMS
Affective slider	Not realising that the slider could be moved to any point on the scale	Instructions were modified to make this clearer
Number of options available per video clip category	One option per category was not enough	Number of options was expanded to three per category
Instructions for selecting video clips	Instructions were unclear, participants did not understand why they were being asked to select three options	Instructions were modified to explain why they were being asked to select video clips
Text on tablet screen	Text is too small	Text was enlarged
Meeting 2		
D-VAMS	Instructions were unclear	Instructions for the D-VAMS were clarified A practice questions was added to get participants used to the slider
D-VAMS and affective slider	Some participants were accidently moving to the next question without adjusting the measures	A new feature was added so that participants could not move on to the next question without adjusting the sliders

Item	Issue raised	Changes made
Intervention content	The newly added music option was too modern, ideas for content were needed for other categories	The group made suggestions which were included in the next iteration of intervention
Meeting 3		
Navigating to the main categories page when browsing video clips	Instruction for how to navigate was unclear	A new 'back to categories' button was added to the video selection page

At the second meeting, the group fed back on the replacement state mood measures, which were the SPANE and D-VAMS. Whilst both were acceptable, the D-VAMS required a better explanation and instructions to make it clear to participants how to respond. The group also generated ideas for appropriate content for some of the video clip categories, particularly the music and stand-up comedy categories. Following the meeting, the instructions preceding the D-VAMS were altered to make it clear that participants can move the slider up and down to change the expression on the face. A practice question was also added so that participants could get used to the slider before the actual questions. Further, a feature was added so that participants could not move on to the next question without adjusting the sliders for both the affective sliders and D-VAMS questions. This was to ensure that participants were clear that they could move the slider to adjust their response, before continuing to the next question. Finally, changes were made to the specific video content that participants were able to choose from, incorporating the suggestions from group members.

The third meeting involved testing the final iteration of the choice-based intervention. Several technical issues were identified, and one participant reported an unclear instruction regarding the option to go back to a previous page, which was noted and later amended to include a ‘back to categories’ button to make it clearer that participants could return to a previous page if the options in a particular category were not appealing to them. Additionally, several aspects of the previous study were identified that participants enjoyed and felt were important to the study experience. They noted that they liked the group format, as it provided a social aspect that was enjoyable. Seeing other people laugh or enjoying the intervention was enjoyable, although for those in the neutral mood condition this was considered confusing or frustrating. When asked about using the tablets, the group agreed that they were easy to use, and noted that for some who had difficulties with writing, the tablets were particularly helpful. Finally, they reported that the presence of a researcher in the room was beneficial if any issues did occur. On the basis of this feedback, these aspects, including the group format, the separate control group and the presence of a researcher, were carried over to the present study.

5.6 Final design

Details of the final study design, following PPI input and taking into account key considerations surrounding the design of the trial, are described in the following section.

5.6.1 *Aims*

i. To investigate whether positive mood differed significantly between usual care and the two interventions (standard fixed-content or choice-based), and which intervention, if any, is superior.

ii. To investigate whether there are differences in four-week antibody responses to the influenza vaccine between the standard fixed-content, choice-based, and usual care groups.

5.6.2 *Design overview*

This study was a three-arm randomised controlled trial. Participants were randomised to one of two experimental conditions, or usual care. The primary outcome was change in mood immediately post-intervention, and the secondary outcome was antibody response at four-weeks follow-up.

5.6.3 *Participants*

Participants were recruited from 13 primary care practices in the East Midlands. The inclusion and exclusion criteria are outlined in Table 5.2. Briefly, to be included participants had to be aged between 65-85 years, received the influenza vaccination in the previous year, and be eligible to receive the 2019/2010 influenza vaccination. Those who did not receive the influenza vaccination in the previous year were excluded. This was to control for variance in baseline antibody levels caused by differences in previous vaccination status.

Table 5.2: Inclusion and Exclusion criteria

Inclusion criteria
• Males and Females aged 65-85 years (inclusive) • Received influenza vaccination for the 2018/19 season • Eligible to receive 2019/20 influenza vaccination as part of usual care • Ability to give informed consent
Exclusion criteria

• Deemed by health care provider to be:
  ○ Too physically frail to participate
  ○ Diagnosed with dementia or other cognitive condition which would make participation difficult
  ○ Insufficient command of English language
  ○ Influenza vaccination contraindicated
  ○ Sufficiently impaired of hearing or vision that exposure to the intervention or control video content as intended would be compromised
  ○ Those for whom the collection of blood samples is contraindicated
  ○ Those who have participated previously in the feasibility study

Participant recruitment began in August 2019, and continued until the desired sample size was reached, with the last participant recruited on 30 October 2019. All baseline visits took place between September and November 2019, and follow-up visits occurred between October and December 2019.

5.6.4 ***Sample size***

A sample size calculation was carried out using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) to detect a medium (d=0.4) effect difference between

the experimental and control arms on the primary outcome with 90% power using separate one-tailed t-tests. This showed that a minimum sample of 253 participants in each experimental arm and 108 participants in the control arm was needed. This will also give 80% power to detect a smaller (d=0.25) difference between the experimental arms in a two tailed t-test. Therefore, the sample size aim was to recruit approximately 650 adults in total to allow for attrition.

5.6.5 ***Intervention***

Standard fixed-content intervention: Participants in the positive mood with fixed-content condition viewed a video designed to increase positive affect. This video was designed as part of a previous study, based on patient and public involvement, focus groups and pilot testing, and has been shown to induce positive mood on the day of vaccination (Ayling et al., 2019). The video included three short comedy clips (clips from The Two Ronnie's; Fawlty Towers; Tim Vine Live stand-up), uplifting music (Jailhouse Rock - Elvis Presley; Happy Together – The Turtles), jokes and positive imagery. The video was approximately 15 minutes in duration.

Choice-based intervention: Participants in the positive mood with choice-based content condition viewed a modified version of the positive mood video in the fixed-content group. The development of this intervention was based on an iterative process following feedback from the PPI group, as outlined in section 5.5. This version was similar in content and duration to the fixed-content intervention, but allowed participants to select the video content from a menu of options. There were four categories of videos (stand-up comedy,

sit-coms, music and 'variety'), and each category had three videos, allowing the participant a total of 12 options. Participants were able to select three videos, each lasting approximately five minutes. Participants were not able to watch the same clip twice. In the stand-up comedy category, the options were extracts from Michael McIntyre, Tim Vine and Victoria Wood. The sit-com category included clips from Fawlty Towers, Only Fools and Horses and The Two Ronnies. In the music category, participants were able to choose between music videos for Elvis Presley (Jailhouse Rock and A Little Less Conversation), Roy Orbison (Pretty Woman and Penny Arcade), and a clip from The Last Night of the Proms. Finally, from the variety category, participants could choose Britain's Got Talent, Strictly Come dancing (both of which included three short clips from the show), and a Terry Wogan option (which included various clips and extracts).

Intervention participants completed pre- and post-questionnaires, and watched videos on hand-held tablet devices using headphones, in groups of approximately six.

Usual care: Participants in the usual care condition did not view a mood enhancing video. They attended their influenza vaccination appointment as normal and were asked to wait for a matched time period in, for example, the practice waiting room. Control group participants completed pre- and post-questionnaires on the same hand-held tablet devices. Instead of a video, participants saw a 15-minute countdown clock with a message to please wait until the countdown has finished. Participants were in groups of approximately six.

5.6.6 ***Measures***

5.6.6.1 Baseline Measures

Chronic stress was measured to assess whether stress influences the relationship between affect and vaccine response. The Perceived Stress Scale (PSS-10; Cohen, Kamarck, & Mermelstein, 1983) was used due to its high internal reliability in a range of populations (Cronbach's alpha = 0.74-0.91) and two-week test re-test reliability (r=0.77; Cohen & Williamson, 1988; Mitchell, Crane, & Kim, 2008; Remor, 2006).The internal reliability in older adults specifically is also high (α = 0.82; Ezzati et al., 2014). The scale was modified in that it asked about these thoughts and feelings for the past three months, rather than one month to capture chronic rather than acute stress. In the present study, internal reliability for the PSS-10 was good (α = 0.88).

Trait affect was measured to assess whether the changes in state affect are influenced by trait affect. The Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) was used due to its high internal reliability in a range of populations, including American university students and employees, non-clinical UK adults, and older adults (Positive Affect Scale (PAS) α = 0.86-0.90; Negative Affect Scale (NAS) α = 0.84-0.87; overall scale α = 0.79) and moderate test re-test reliability (r = 0.47-0.86 for the PAS, and r = 0.39-0.71 for the NAS; Crawford & Henry, 2004; Von Humboldt, Monteiro, & Leal, 2017; Watson, Clark, & Tellegen, 1988). Internal reliability in the present study was excellent for both the positive (α = 0.91) and negative (α = 0.90) subscales. In light of the ongoing interest in the constructs of positive and negative affect, both individually and in terms of the balance between the two (discussed in section 2.3.2), an index of affective balance, defined as relative

levels of negative and positive affect, was also created using the PANAS, based on the methods described in Hassett et al. (2008). Four distinct affect balance styles were created, including 'healthy' (high positive affect and low negative affect), 'low' (low positive and low negative affect), 'reactive' (high positive and negative affect), and 'depressive' (low positive affect and high negative affect). Categories were calculated using cut-offs based on population means for the PANAS positive and negative subscales (reported in section 6.5.3). Those scoring above the mean were classed as high on that measure, and those below the mean were classed as low.

Health status was assessed to control for differences in health between participants. The Short Form Health Survey (SF-12; Ware Jr, Kosinski, & Keller, 1996) was used to assess both physical and mental health. This measure was selected over the SF-36 due to its reduced burden. It has good test-retest reliability in a general UK population (α = 0.89 for the physical component summary [PCS], and 0.77 for the mental component summary [MCS]) (Ware Jr et al., 1996), and its internal reliability is generally high in range of populations, including those with back pain, and those who have had a stroke (α ≥ 0.77 for PCS, α ≥ 0.80 for MCS; Lim & Fisher, 1999; Luo et al., 2003). In the general elderly population specifically (aged >75 years), reliability is also high (α = 0.85 for the PCS and α = 0.83 for the MCS; Jakobsson, Westergren, Lindskov, & Hagell, 2012). In the present study, internal reliability was good for the mental health subscale (α = 0.86) and excellent for the physical health subscale (α = 0.90).

5.6.6.2 Primary Outcome Measures

State affect was measured to assess changes in pre- and post-intervention mood. One measure of state affect was used as the primary outcome measure:

- The Affective Slider is a pictorial digital scale that has two separate sliders measuring pleasure and arousal (Betella & Verschure, 2016). This scale does not require written instructions and can be used on digital devices. The Affective Slider has previously been validated through systematic comparison with the Self-Assessment Manikin, in which the Affective Slider was shown to be favourable in the assessment of pleasure and arousal (Betella & Verschure, 2016). Given that the pleasure slider subscale was previously used in the feasibility study and found to significantly improve in the positive mood intervention group, this was used as the primary state affect outcome measure.

5.6.6.3 Secondary Mood Outcome Measures

- The Affective Slider arousal subscale (described above) was used to assess changes in state arousal from pre- to post- intervention.
- The Scale of Positive and Negative Experience (SPANE) was used to assess positive and negative feelings (Diener et al., 2010), due to its high internal reliability (α = 0.89-0.92; (Diener et al., 2010; Li, Bai, & Wang, 2013) and moderately high four-week test re-test reliability (r = 0.68) in both university student and working adult populations (Diener et al., 2010). In the present study, the SPANE positive subscale was good to excellent at the two time-points (α = 0.89 and 0.93), and the SPANE negative subscale was good at both time-points (α = 0.83 at both time-points).

- The Dynamic Visual Analogue Mood Scales (D-VAMS) (Barrows, 2016) was used as a non-verbal way to assess state mood. The scale consists of sliders that can be adjusted so that the expression best reflects the participant's own mood. For this study, only the sad-happy and sleepy-alert dimensions were used to assess mood and arousal levels. Internal reliability of the D-VAMS in a population of stroke survivors with a mean age of 63.8 years is high (α=0.95; Barrows & Thomas, 2018).

5.6.6.4 Secondary Outcome Measures

Immune response to vaccination was measured using titre testing of serum antibodies to determine whether there were any differences between the three groups in this outcome. There are several ways in which this can be done, including microarrays, bead-based assays, enzyme-linked immunoassays (ELISA), and hemagglutination Inhibition assays (HAI). The most commonly used methods in this specific area of research are ELISAs and HAIs, however due to several factors, including the number of samples requiring processing for the For-ME study (over 650 samples at two time-points), the lower consumable requirements, and more specific and sensitive outputs, the ELISA method was considered the most suitable for the present study. More details of the ELISA methodology are outlined in section 5.7.

5.6.7 ***Randomisation***

Participants were randomised on a 2:2:1 ratio to one of the two experimental arms or to usual care, using a third-party randomisation service. Allocation was done by a third party, so that the researchers involved were blind to the allocation of participants to the two experimental arms. Due to the nature of

the usual care arm, which did not receive a video positive mood intervention, it was not possible to blind researchers to this condition.

5.6.8 *Procedure*

Figure 5.1 outlines the timeline of the study procedure. Ethical approval and research governance approval was obtained prior to study commencement, on the 2 April 2019 (REC: 19/EM/0081). The study was also portfolio adopted by the Clinical Research Network on 11 March 2019 (UKCRN Ref: 41450) and registered on ClinicalTrials.gov on 30 April 2019 (Identifier: NCT03956329). GP practices conducted the search for eligible participants, and sent out an invitation letter and information sheets detailing the study to those deemed eligible. All searches and invitations were sent between 1 August 2019 and 27 September 2019. The information sheet was designed in a way so as to not create an expectation of the study for potential participants. Specifically, whilst the information sheet informed participants about the broad aims of the study, it did not detail the direction of the hypotheses or outline the two intervention arms in detail. Potentially interested participants were then able to return a reply slip to the research team with contact information. Based on previous research, a response rate of approximately 10% was expected (Ayling et al., 2018; 2019). The research team contacted potential participants to answer any questions and arrange a suitable time for their first visit to the GP practice. They were also sent a baseline questionnaire (described above) to either return by post or bring in to the first visit.

On the day of vaccination, participants had their height and weight measured, and a blood sample taken to assess baseline IgG antibody levels. They then

completed the pre-intervention questionnaires and watched one of the intervention videos or underwent usual care, depending on group allocation.

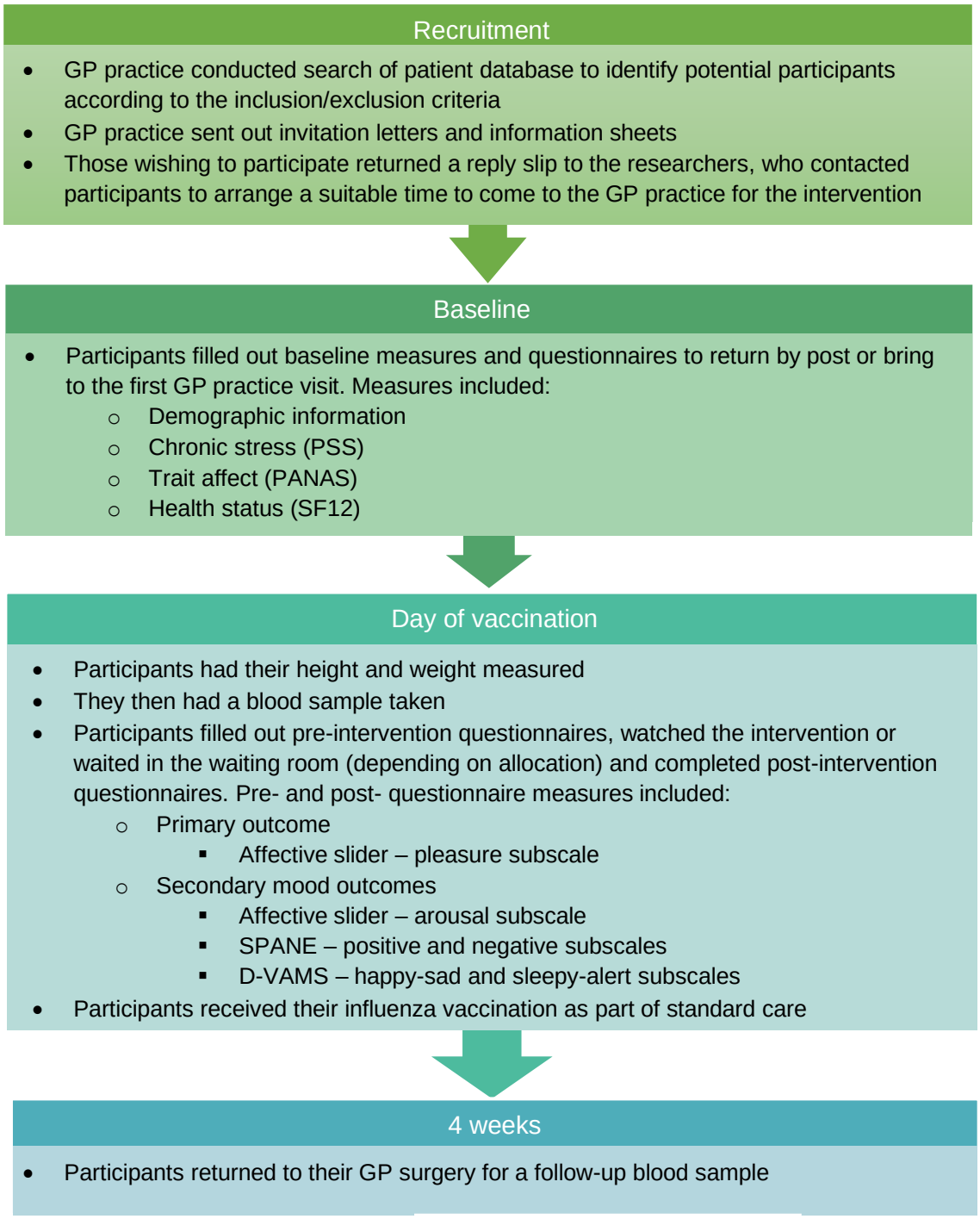


Figure 5.1: Timeline of study

Participants then completed the post-intervention questionnaires and received their influenza vaccination.

Four weeks after vaccination, participants returned to the GP practice for the second visit. This visit included a blood sample only, to assess follow-up IgG antibody levels. The total active duration of the trial was three months, with each participant being actively involved for a one-month period.

5.7 Blood Analysis

Blood Samples were assessed for influenza vaccine antigen specific antibodies via ELISA in accordance with published protocols (Ayling, Vedhara, & Fairclough, 2018; World Health Organization, 2011). A process of optimisation of the ELISA protocol took place, which is not detailed here due to space constraints. This was necessary for two reasons. Firstly, both the H1N1 and the H3N2 influenza vaccine strains were new to the 2019/2020 vaccination. Secondly, the vaccination was adjuvanted, whereas previous vaccinations were not. Both of these factors can result in differences in immunogenicity, thus optimisation specific for this adjuvanted trivalent 2019/2020 influenza vaccination was required. A series of experiments were carried out as part of this optimisation process, during which several changes to the original protocol were made, including standardised vortexing, standardised batches of antigens, temperature control, daily preparation of Human IgG, trialling of different antigen and sera concentrations and reduced drying times. However, despite these adjustments, the protocol was unable to produce reliable standard curves. At this point, there was a substantial 6-month delay to the laboratory process, due to the COVID-19 global pandemic.

This had a number of impacts on the laboratory environment when activities were resumed, including laboratory access becoming severely restricted. As a result, priorities for the assay changed, with emphasis on producing an assay that had a shorter total duration, as well as addressing the issues surrounding the reliability of the standard curve. Therefore, alternative assay controls to the previously used standard curve were trialled, including the use of a pseudo-standard curve using samples to interpolate against was trialled, and the use of a common set of samples across all days to adjust all other samples of the plate to normalise using regression. The final protocol employed the latter method, with adjustment using regression resulting in excellent inter-assay variation.

The full protocol can be found in Appendix F. The main differences between the initial protocol and this final protocol included measures to reduce the length of the protocol (coating and blocking plates in advance, use of a different conjugated anti-human IgG meaning that additional steps involving streptavidin HRP was not needed, reduced serum incubation time from two to one hours), and the use of control samples rather than a standard curve. As a result of advance coating and blocking, the most plates coated on a single day was 15 (one plate per antigen, for five consecutive testing days). Each sample was assayed in duplicate. In terms of the common control samples, a total of 24 samples were included on every single plate for every run and formed the basis of the statistical regression. The last well of each plate was left as a negative control with no sample. Thus, the total number of non-control samples per run was 167. The value used for analysis was the adjusted optical density read by an optical scanner (Promega GloMax). Higher scores

indicate greater antibody levels. Section 6.3.5 will discuss how this is operationalised in more detail.

5.8 Chapter summary

This chapter described the development of a three-armed randomised controlled clinical trial, designed to assess and compare the effects of two different interventions on positive mood enhancement on the day of influenza vaccination and whether these interventions, in turn, affected the magnitude of the antibody response to vaccination. Whilst one intervention was taken from a previous feasibility study, the other was developed based on PPI group feedback and aimed to assess whether incorporating participant choice into the intervention lead to greater increases in both positive mood, and vaccine response, than the fixed content intervention and/or usual care. Therefore, key outcome measures included both positive mood, and vaccine specific IgG antibody levels at four-weeks post-vaccination. The next chapter outlines the approach to quantitative data analysis and presents results of the For-ME study analysis in terms of the two previously outlined aims.

6 Chapter 6: The For-ME study: Randomised controlled clinical trial results

6.1 Chapter introduction

This chapter presents the results of the For-ME trial, assessing the two primary research aims outlined in Chapter 5. It first outlines several issues pertaining to the treatment of data during the analysis process, including testing of statistical assumptions, missing data, testing for baseline differences, measuring antibody response, and accounting for baseline values. Following this discussion, a description of the study participants is provided, before the results addressing both of the aims are presented. A full recap of the key findings and the implications of these, as well as some strengths and limitations of the study that should be considered, will then be presented in the next chapter, following the presentation of some exploratory analyses.

6.2 Background

As outlined in this thesis, previous evidence has shown that a brief positive mood intervention is able to significantly improve positive mood in older adults on the day of vaccination, and may be associated with improved antibody response to vaccination. The present trial now sought to address several outstanding questions, including how the previously trialled positive mood intervention (standard fixed-choice intervention) compares to usual care, and whether it can be improved upon using choice to maximise potential mood increases. This chapter therefore presents the results from the For-ME study.

6.3 Treatment of data

6.3.1 *Testing assumptions*

6.3.1.1 Parametric data assumptions

Several data distribution assumptions underlying statistical tests were examined depending on the specific analyses being carried out. For all analyses univariate outliers were assessed using the process outlined by Tabachnick and Fidell (2001). For tests of grouped data, outliers were identified separately within each group, whereas for tests of overall data, outliers were identified for the overall cohort. To identify univariate outliers, standardised scores (z scores) were generated, and any cases with scores above 3.29 or below -3.29 were classified as outliers and were subsequently removed from the analysis and treated as missing data. Where applicable, such as when running analyses of covariance (ANCOVAs), multivariate outliers were identified by generating Mahalanobis distance values from an initial regression analysis. The chi-square distribution table was then used to identify a critical value where $p < .001$ and the degrees of freedom is equal to the number of variables being examined (Tabachnick & Fidell, 2001). Any cases with scores over this value were classed as multivariate outliers and were also removed.

Normality of distribution was assessed where necessary using visual inspection of histograms. Antibody levels for all antigen strains at both time points were found to have significant positive skew and were log (base 10) transformed. This transformation resulted in appropriately normal distributions upon re-analysis of histograms, thus the transformed scores were used in all subsequent analyses. For all mood outcomes, histograms showed significant

skew and so transformations including $\log_{10}$, $\log_2$, square root and reciprocal transformations were performed, however these did not resolve the skew to result in acceptable normal distributions. Therefore, where normally distributed variables were required, non-parametric versions of tests were performed as sensitivity analyses. These can be found in Appendix H.

Homogeneity of variance was assessed when comparing the three groups, using Levene's test of equality of error variances. Significant values ($p < .05$) indicated unequal variances.

6.3.1.2 ANCOVA specific assumptions

As outlined in section 6.4, ANCOVAs were used for a number of analyses, therefore several additional considerations specific to this methodology were required.

Linearity was assessed visually using scatterplots for each dependent and covariate outcome. Upon visual inspection, scatterplots indicated a linear relationships between each dependent and covariate pair, for both mood-related and antibody outcomes. Normality of residuals was assessed by producing and then plotting the standardised residual on a histogram for each dependent outcome in an ANCOVA model including the corresponding covariate. Normality was assessed by visually inspecting each histogram, which were found to be acceptably normal for each outcome. Homogeneity of regression slopes was assessed during the ANCOVA analyses, by building terms in the univariate model, adding both the covariate and covariate by

independent variable interaction into the model. A significant covariate by independent variable interaction ($p < .05$) indicated that this assumption was violated. Independence of the covariate and treatment effect was assessed using one-way analyses of variance (ANOVAs) or the Kruskal-Wallis H test for data that was not normally distributed, with significant values ($p < .05$) indicating significant differences between groups in the covariate variable, indicating that the assumption would be violated. As above, where any ANCOVA specific assumptions were violated, a non-parametric version of the test was performed as a sensitivity analysis, and can be found in Appendix H.

6.3.2 ***Missing data***

Given relatively low levels of missing data (between 0-2.60% for demographic variables, 1.99-5.35% for items on health-related and psychological variables, 1.22-3.67% for pre- and post-intervention state mood variables, and 0.61% for pre-vaccination and 10.92% for post-vaccination antibody variables), no imputation was performed. Instead, missing data were coded as missing by assigning a value (-99). Thus, if any item was missing in a scale, the whole scale was counted as missing for the participant, even if other items on the measure were reported.

6.3.2.1 Per-protocol and intent-to-treat analyses

The intent-to-treat analysis included all participants who met the inclusion criteria and consented to take part in the study. Some missing data occurred for baseline measures due to incomplete questionnaire responses (SF12 physical n= 68 [10.40%]; SF12 mental n=68 [10.40%]; PANAS positive n=59 [9.02%]; PANAS negative n=45 [6.88%]; PSS n=37 [5.66%]). Missing state

mood data occurred on the day of the intervention due to some technical issues with tablets resulting in responses not being saved (n=40 [6.11%]). Additionally, some antibody specific missing data occurred at pre- and post-vaccination due to not being able to obtain a sufficient blood sample (n=29 [4.43%]). For the per-protocol analyses, participants were excluded where there were reasonable grounds to believe that they did not receive the intervention as intended. For example, some participants experienced technical issues with the tablet devices (n=6), resulting in them not receiving the 15-minute intervention in full, or receiving the incorrect intervention (n=2). Other exclusions from the per-protocol analysis included participants who attended a session where one participant brought their puppy into the session with them (n=4), participants who were observed watching another participants' tablet device with a different group allocation (n=1), and a participants who experienced interruptions such as taking a phone call during the intervention (n=1), having to leave early (n=1), no longer wanting to watch the video clips (n=2), or going to reception to make a GP appointment during the intervention session (n=1). See Figure 6.1 for participant flow, including drop-outs and exclusions throughout the study. In the remainder of this section, the intention-to-treat analyses will be presented, and any instances with notable differences between the intention-to-treat and per-protocol analyses will be highlighted.

6.3.3 *Testing for baseline differences*

Whilst it has previously been considered common practice to test for significant differences in baseline values in randomised controlled trials, several researchers have advocated for discontinuing this behaviour (De Boer, Waterlander, Kuijper, Steenhuis, & Twisk, 2015). Indeed, the

CONSORT 2010 guidance states that this should not be done for randomised controlled studies (Moher et al., 2012). This is because in randomised controlled trials, any difference observed between groups at baseline will necessarily be due to chance, due to the nature of randomisation (Altman, 1985). Thus, testing for baseline group differences equates to assessing the probability of something being due to chance, whilst knowing that it is due to chance. Further, a p value of 0.05 means that one out of 20 tests would be expected to be significant by chance, therefore when many baseline characteristics are tested a significant difference in one of these is to be expected. Indeed, Van Breukelen and Van Dijk (2007) state that when treatment assignment is random and there is no selective drop-out, adjustment for baseline differences is not necessary.

Based on the above, in the following analyses, no tests for significant differences at baseline were conducted, and therefore no adjustments have been made to any analyses on the basis of baseline differences.

6.3.4 ***Accounting for baseline values***

While no tests for significant differences *between groups* at baseline were performed, it is nevertheless important to understand and account for how baseline scores can predict later scores *within individuals*. Baseline values are often correlated to and highly predictive of post-intervention values, and thus should be taken into consideration in analyses of post scores. Indeed, whilst there are some advantages to post-intervention comparisons, namely ease of interpretation, shorter time requirements for analysis and minimal influence of a secondary outcome, not only do they not account for this relationship, but

they are also less precise and have less statistical power compared to methods that do account for this relationship (Zhang et al., 2014). Several methods are available, including computing a change score and comparing between groups using a method such as an ANOVA, or including baseline scores as covariates in an ANCOVA analysis. In comparisons of the two methods, several authors have concluded that in randomised studies with baseline and follow-up scores, ANCOVAs are the superior and preferred analysis method, due to increased power, precision and reduced bias (Egbewale, Lewis, & Sim, 2014; Tu, Blance, Clerehugh, & Gilthorpe, 2005; Tu, Baelum, & Gilthorpe, 2008; Van Breukelen, 2006; Vickers & Altman, 2001). Based on this, the ANCOVA approach, with baseline values included as covariates, was adopted for the following analyses of both mood and antibody outcomes. However, given the aforementioned benefits of analyses based on post-intervention scores only, primarily the ease of interpretation, analyses using this method were also conducted and can be found in Appendix G.

Whilst including baseline antibody levels as covariates may be sufficient, there is some concern that this may still result in an over- or under-estimation of vaccine effectiveness, given the strong association between pre- and post-vaccination antibody levels. To account for this, a method has been proposed whereby a correction is made to post-vaccination scores, by performing a linear regression with log transformed post-vaccination antibody levels as the dependent variable and log transformed pre-vaccination antibody levels as a predictor variable (Beyer, Palache, Lüchters, Nauta, & Osterhaus, 2004). The regression slope from this is then used to calculate baseline adjusted post-vaccination scores. In this thesis, this adjustment was carried out as sensitivity analyses in addition to the ANCOVA, and can be found in Appendix H.

6.3.5 *Operationalising antibody response*

The effectiveness of vaccines can be assessed in several ways, and indeed, in the literature a range of definitions and operationalisations have been used. For instance, some measures of vaccine effectiveness do not examine antibody outcomes, but instead employ test-negative designs, such as effectiveness statistics published by Public Health England. These designs use an exposure odds ratio, which is calculated by determining the odds of vaccination amongst those who test positive for influenza and those who test negative, before being transformed into a percentage representing vaccine effectiveness (Lewnard, Tedijanto, Cowling, & Lipsitch, 2018).

Of the studies focusing on immunological response to vaccination as an indicator of vaccine effectiveness, in particular influenza IgG antibody response, there are several methods of assessment, which are closely linked to the method of analysis. When using the ELISA method, as used in the current study, a continuous measure of vaccine response (optical density) is produced. This represents the concentration of antibody in the sample, with higher optical densities representing higher antibody concentrations. There are no clinical cut-offs associated with ELISA optical densities, therefore rather than being dichotomised as being protected or not, higher optical densities are taken as an indicator of greater clinical protection (Coudeville et al., 2010). Antibody response from ELISAs can be reported in terms of post-vaccination levels only, or in terms of the change in antibody levels from baseline to post-vaccination (e.g. Ayling 2019). Whilst post-vaccination levels can tell you valuable information regarding absolute antibody levels following

vaccination, they do not take into account pre-vaccination levels. In influenza vaccination in particular, this is important as it is expected that those who have previously received an annual influenza vaccine or been exposed to the influenza virus, are likely to have existing circulating antibodies, and this will not be the same across individuals. This is certainly true in the present study, where all participants were required to have had the previous years' vaccine as part of the inclusion criteria. Further, there is evidence that lower pre-vaccination antibody levels may be associated with greater increases at post-vaccination (Sasaki et al., 2008).

A further consideration regarding the assessment of antibody response to vaccination was whether responses to each antigen strain within the vaccine should be considered separately or as a composite. Whilst the later has been employed previously (e.g. Segerstrom et al., 2012), it makes the assumption that the different strains would respond similarly. However, as noted in Chapter 3, this is not always the case, with evidence of differential effects of various psychological and behavioural factors on antibody response across the three strains (e.g. Edwards et al., 2006; Keylock et al., 2007; Kohut et al., 2004, 2005). Therefore, in line with previous research and to account for potential differences in antibody response according to antigen strain, the approach taken in the chapter was to consider each strain separately.

6.4 Data analysis

Quantitative data was analysed using SPSS. To examine differences between the intervention and usual care groups in the primary and secondary mood outcomes, as well as four-week antibody responses, a series of one-way

ANCOVAs were used. Several exploratory analyses were also carried out (see Chapter 7). A series of linear regressions were used to assess (a) whether trait and/or chronic states were predictive of the effect of the intervention, (b) whether state positive affect change from pre- to post-intervention was predictive of baseline-adjusted antibody levels, and (c) whether trait and/or chronic states predicted baseline adjusted antibody levels. Tertiary splits followed by a series of one-way ANOVAs, or the non-parametric equivalent (i.e., Kruskal-Wallis test) were also used to examine differences between (a) low, middle and high scoring participants on trait and/or chronic state measures in terms of change in state affect, and (b) those with worse/no change, minimal change and those who had improved state affect scores from pre- to post-intervention, in terms of antibody response. Additionally, a median split, followed by a series of independent t-tests were used to assess whether there were differences between those scoring lower or higher on each trait/chronic state measure in antibody response. Finally, the relationship between positive and negative mood was assessed using one-way ANCOVAs and ANOVAs to investigate whether there were significant differences in four affective balance groups in terms of post-intervention state affect, change in state affect, and four-week antibody response.

6.5 Descriptive statistics

6.5.1 *Recruitment*

A flow diagram of participants through the study can be found in Figure 6.1. Of the 7025 older adults invited to participate, 848 returned an interest slip, with an uptake rate of 12.07%. Of those 705 (83.1%) were subsequently

randomised, and 654 (77%) consented. Drop-out between randomisation and consent was due to randomisation needing to take place at the time of appointment booking for the first visit to the GP practice, which was in advance of the visit, during which formal written consent was obtained. This process was necessary due to the requirement to have separate sessions for usual care participants, as discussed in Chapter 5. Thus, whilst 705 participants were randomised and allocated to one of the three groups, not all attended their scheduled sessions to provide written consent.

A total of 654 participants attended the baseline appointment, at which participants provided written consent. Retention at the four-week follow-up was high, with 94% of the consented participants, and 87.5% of those originally randomised attending the follow-up session. Reasons for drop-out at the first study session were similar between groups, and included not attending the appointment for unknown reasons (14 participants), illness (12 participants), receiving the influenza vaccine prior to the first study session (6 participants), time constraints (3 participants), changing their mind about taking part (4 participants), no longer being able to attend the scheduled session and not being available for any alternative (11 participants), and wanting the vaccine earlier than the study session dates (1 participant). Attendance to the follow-up visit was similar between groups (standard group 93.56%, choice group 94.32%, usual care 96.03%). Thus, drop-out between initial contact and the first session was 7.23% and drop-out between the first and second session was 5.7%.

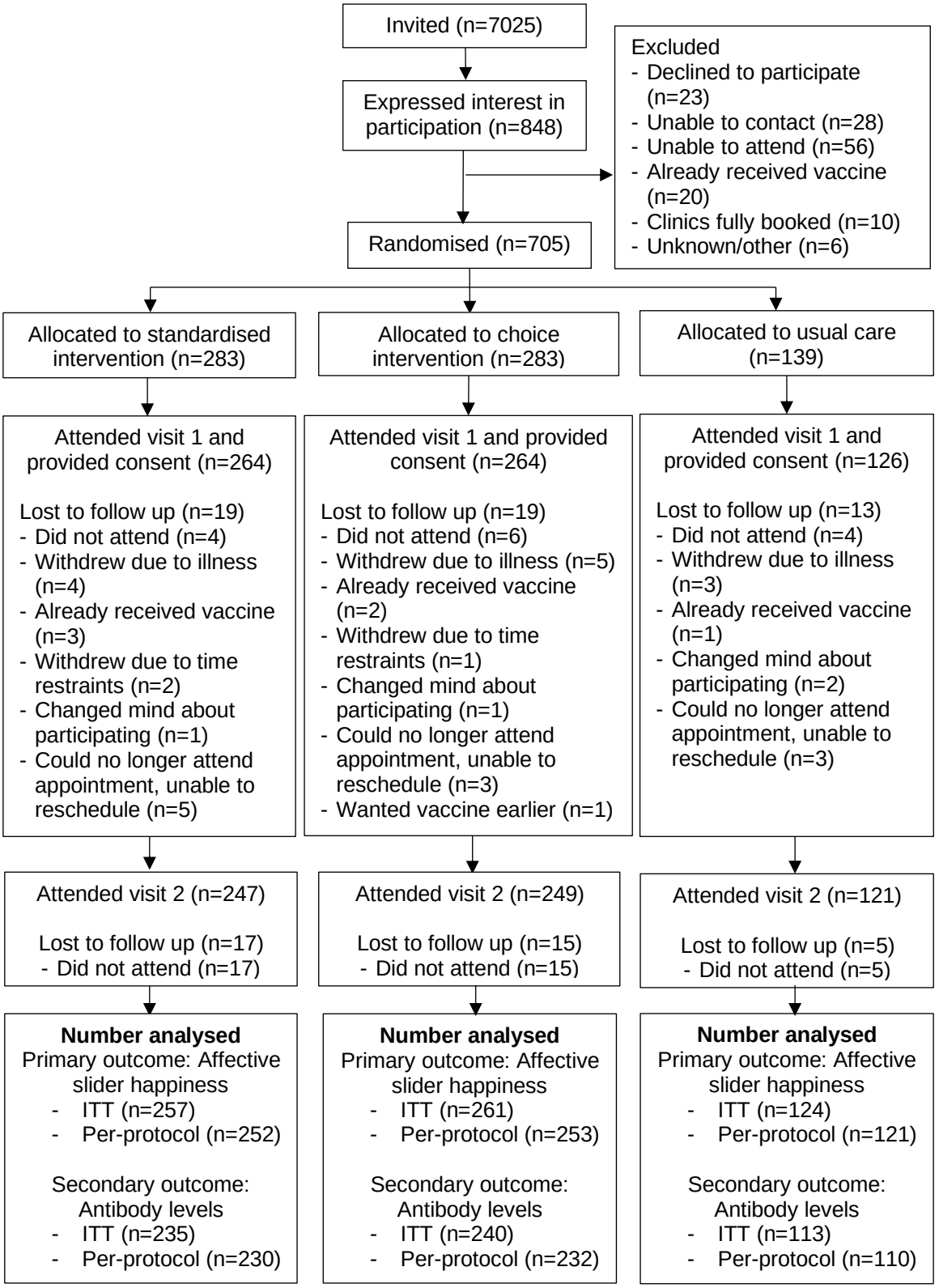


Figure 6.1: Flow of participants through the study

6.5.2 *Participant demographics*

Participant demographic information for the intent-to-treat population can be found in Table 6.1. The mean age of all participants was 73.39 years old (SD = 5.10). Just over half the cohort were female (53.67%), predominately white (96.33%), non-smokers (92.97%), live independently (93.43%), were educated to school level (47.86%), and were married (64.53%). The average body mass index (BMI) was 27.68, which corresponds to a definition of overweight and is comparable to the average BMI of adults aged 65 years and older in England in 2019 (28.3; National Statistics, 2020).

Table 6.1: Participant demographics at baseline for each intervention group and in total in the intention-to-treat population

	Standard	**Choice**	**Usual care**	**Total**
		Mean (SD), *n*		
Age	73.20 (5.11), 264	73.28 (4.91), 264	74.02 (5.43), 126	73.39 (5.10), 654
Height (cm	167.66 (10.34), 263	166.24 (10.35), 263	166.76 (9.69), 125	166.91 (10.10), 651
Weight (kg	76.66 (16.04), 263	77.34 (16.19), 263	78.89 (20.29), 125	77.36 (16.99), 651
BMI	27.21 (4.95), 263	27.92 (5.08), 263	28.13 (5.76), 125	27.68 (5.17), 651
		Frequency (%)		
Gender				
Male	127 (48.11)	117 (44.32)	59 (46.83)	303 (46.33)
Female	137 (51.89)	147 (55.68)	67 (53.17)	351 (53.67)
Did not respond	0 (0)	0 (0)	0 (0)	0 (0)
Ethnicity				
White	254 (96.21)	255 (96.59)	121 (96.03)	630 (96.33)
Black	2 (0.76)	0 (0)	0 (0)	2 (0.31)
Asian	1 (0.38)	0 (0)	2 (1.59)	3 (0.46)
Mixed	1 (0.38)	0 (0)	0 (0)	1 (0.15)
Other	1 (0.38)	0 (0)	0 (0)	1 (0.15)
Did not respond	5 (1.89)	9 (3.41)	3 (2.38)	17 (2.60)
Smoking				
No	251 (95.08)	240 (90.91)	117 (92.86)	608 (92.97)
Yes	9 (3.41)	17 (6.44)	6 (4.76)	32 (4.89)
Did not respond	4 (1.52)	7 (2.65)	3 (2.38)	14 (2.14)

	Standard	Choice	Usual care	Total
Lives independently				
Yes	247 (93.56)	247 (93.56)	117 (92.86)	611 (93.43)
No	13 (4.92)	10 (3.79)	6 (4.76)	29 (4.43)
Did not respond	4 (1.52)	7 (2.65)	3 (2.38)	14 (2.14)
Education				
School	119 (45.76)	127 (48.11)	67 (53.17)	313 (47.86)
University (undergraduate)	27 (10.23)	25 (9.47)	17 (13.49)	69 (10.55)
University (postgraduate)	45 (17.05)	50 (18.94)	20 (15.87)	115 (17.58)
Other	68 (25.76)	54 (20.45)	19 (15.08)	141 (21.56)
Did not respond	5 (1.89)	8 (3.03)	3 (2.38)	16 (2.45)
Marital status				
Married	173 (65.53)	170 (64.39)	79 (62.70)	422 (64.53)
Single, never married	8 (3.03)	11 (4.17)	9 (7.14)	28 (4.28)
Separated/ divorced	35 (13.26)	29 (10.98)	10 (7.94)	74 (11.31)
Widowed	36 (13.64)	39 (14.77)	19 (15.08)	94 (14.37)
Co-habiting	8 (3.03)	7 (2.65)	6 (4.76)	21 (3.21)
Did not respond	4 (1.52)	8 (3.03)	3 (2.38)	15 (2.29)

6.5.3 *Baseline health related and psychological characteristics*

Table 6.2 shows the baseline health related and psychological characteristics of the intention-to-treat population between groups and overall. The average mental and physical health scores as measured by the SF12 were 53.13 and 45.81 respectively, both of which are similar to previously reported normative data for those in the UK aged over 65 years (Mean = 54.6 and 46.4 respectively; Macran, Weatherly, & Kind, 2003). Trait mood as assessed by the PANAS showed that the average trait positive mood score was 34.62, whereas the negative mood scores was 15.05, both of which are similar to those reported in a UK general population sample (Mean = 31.31 and 16.00, respectively; Crawford & Henry, 2004). Average chronic stress measured using the Perceived Stress Scale over the past three months was 12.54,

which is comparable to previously reported normative data in adults aged 65 years and over in the US (Mean = 12.0; Cohen & Williamson, 1988) .

Table 6.2: Baseline health related and psychological characteristics (mean, SD, n)

	Standard	Choice	Usual care	Total
Mental health (SF12)	53.24 (8.80), 240	53.46 (9.24), 236	53.13 (10.20), 110	53.31 (9.24), 586
Physical health (SF12)	46.96 (10.70), 240	45.68 (11.27), 236	43.59 (11.09), 110	45.81 (11.05), 586
Trait positive mood (PANAS)	34.78 (7.56), 240	34.70 (7.70), 246	34.12 (7.91), 109	34.62 (7.67), 595
Trait negative mood (PANAS)	14.99 (6.08), 249	15.04 (5.88), 245	15.19 (5.75), 115	15.05 (5.93), 609
Perceived stress over the past 3 months (PSS-10)	12.59 (7.24), 245	12.58 (7.29), 255	12.34 (7.01), 117	12.54 (7.21), 617

6.6 Results

6.6.1 *Aim 1: To investigate whether positive mood differed significantly between usual care and the two interventions (standard fixed-content or choice-based), and which intervention, if any, is superior.*

6.6.1.1 Research question

1.1 Are there significant differences between the standard fixed-content intervention, choice-based intervention and usual care arms in terms of each of the mood-related outcomes at post-intervention?

6.6.1.2 Hypotheses

Based on results of the previous feasibility study regarding the effectiveness of the standard fixed-content intervention, and research regarding the potential benefits of choice, it was hypothesised that:

(i) Both the standard fixed-content and choice-based interventions would result in significantly greater post-intervention positive mood compared to the usual care condition.

(ii) The choice condition would result in significantly greater post-intervention positive mood scores compared with the standard fixed-content intervention.

6.6.1.3 Analyses

ANCOVAs were conducted to assess whether there were significant differences in state positive affect scores on primary and secondary mood outcomes, between all of the three groups compared to each other.

6.6.1.3.1 Primary outcome

Table 6.3 and Figure 6.2 show the mean pre- and post-intervention scores for the primary outcome in each of the three study arms.

To assess whether these group differences at post-intervention were significant, a one-way ANCOVA was conducted, with the pre-intervention score included as the covariate. This analysis demonstrated that there was a significant effect of group allocation on post-intervention scores after controlling for the effect of pre-intervention score for the primary outcome

(Table 6.5; $F(2, 612) = 18.98$, $p < .001$, partial $\eta^2 = .058$). Planned contrasts revealed that receiving the choice-based intervention significantly increased scores on the affective slider pleasure outcome compared to receiving usual care, $t(612) = -5.95$, $p < .001$, $r = .234$, but not compared to the standard fixed-content intervention, $t(612) = -0.90$, $p = .368$, $r = .036$ (see Table 6.6).

6.6.1.3.2 Secondary mood outcomes

Table 6.4 shows the mean pre- and post-intervention scores for the secondary state mood outcomes in the three intervention groups. This is also illustrated in Figure 6.2.

Table 6.3: Pre- and post-intervention scores on the primary outcome measure (mean, SD)

	Standard			Choice			Usual care		
	Pre	Post	Adj. Post*	Pre	Post	Adj. Post*	Pre	Post	Adj. Post*
Affective slider: pleasure	79.22 (20.24)	86.83 (14.28)	86.89 (0.59)	80.76 (17.67)	88.23 (12.91)	87.65 (0.59)	77.11 (23.07)	80.10 (21.06)	81.45 (0.86)

* Post-intervention scores adjusted for pre-intervention scores. Values are mean and standard error.

Table 6.4: Pre- and post-intervention scores for secondary mood outcomes (mean, SD)

	Standard			Choice			Usual care		
	Pre	Post	Adj. Post*	Pre	Post	Adj. Post*	Pre	Post	Adj. Post*
Affective slider: arousal	84.99 (13.76)	88.51 (11.97)	88.00 (0.45)	84.08 (16.98)	88.99 (13.06)	89.13 (0.44)	82.54 (20.06)	84.31 (19.28)	86.42 (0.65)
D-VAMS: happy-sad	78.00 (16.61)	86.13 (13.15)	86.47 (0.56)	80.12 (14.67)	86.85 (12.59)	86.14 (0.56)	76.78 (19.19)	78.81 (18.54)	79.37 (0.81)
D-VAMS: sleepy-alert	78.33 (13.77)	82.87 (13.74)	83.45 (0.52)	78.95 (14.96)	84.69 (13.08)	84.50 (0.52)	76.43 (19.68)	79.36 (16.53)	80.17 (0.76)
SPANE: positive	22.13 (5.00)	24.04 (4.78)	24.17 (0.17)	22.64 (4.46)	24.79 (4.26)	24.59 (0.17)	22.07 (5.23)	22.74 (5.11)	23.00 (0.25)
SPANE: negative	7.25 (2.07)	6.62 (1.32)	6.61 (0.07)	7.09 (1.71)	6.63 (1.47)	6.74 (0.07)	7.89 (2.88)	7.43 (2.24)	7.15 (0.11)

* Post-intervention scores adjusted for pre-intervention scores. Values are mean and standard error.

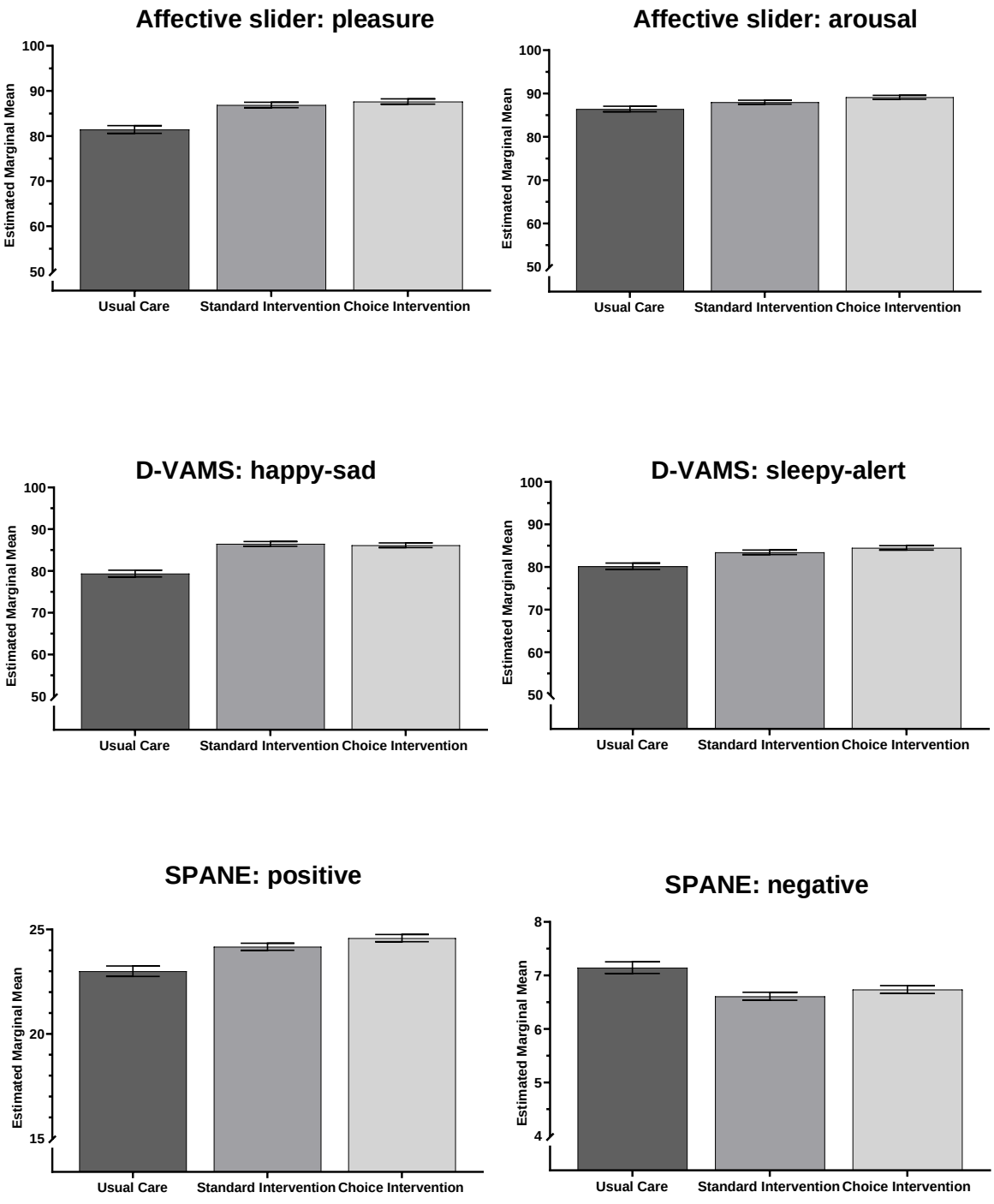


Figure 6.2: Post-intervention mood scores adjusted for pre-intervention scores by group. Bars are mean scores. Error bars are 95% confidence intervals.

To assess whether these group differences at post-intervention were significant, a series of one-way ANCOVA's were performed, with baseline values for each outcome included as a covariate. These demonstrated that there was a significant effect of group allocation on post-intervention scores after controlling for the effect of pre-intervention scores for each of the five outcomes (see Table 6.5; slider-arousal: $F(2, 611) = 6.09$, $p = .02$, partial $\eta^2 = .020$; DVAMS happy-sad: $F(2, 605) = 29.54$, $p < .001$, partial $\eta^2 = .089$; D-VAMS sleepy-alert: $F(2, 601) = 11.29$, $p < .001$, partial $\eta^2 = .036$; SPANE positive: $F(2, 622) = 13.62$, $p < .001$, partial $\eta^2 = .042$; SPANE negative: $F(2, 608) = 8.48$, $p < .001$, partial $\eta^2 = .027$).

Planned contrasts were carried out to assess where these differences lay (see Table 6.6). For all five secondary outcomes, the contrasts revealed that receiving the standardised and choice interventions significantly increased post-intervention scores compared to the usual control group. However, there were no significant differences between the standardised and the choice groups.

Table 6.5: Parametric ANCOVA to compare the three intervention groups in terms of the primary outcome and secondary mood-related outcomes at post-intervention with pre-intervention values included as covariates

	df	***F***	***p***	**Partial η^2**
Affective slider: pleasure	612	18.98	< .001	.058
Affective slider: arousal	611	6.09	.020	.020
D-VAMS: happy-sad	605	29.54	< .001	.089
D-VAMS: sleepy-alert	601	11.29	< .001	.036
SPANE: positive	622	13.62	< .001	.042
SPANE: negative	608	8.48	< .001	.027

Table 6.6: Planned contrasts from the parametric ANCOVA to compare the choice and usual care group and the choice and standard intervention groups in terms of the primary outcome and secondary mood-related outcomes

	Choice vs usual care				Choice vs standard			
	t	***p***	**Partial η^2**	**r**	***t***	***p***	**Partial η^2**	**r**
Affective slider: pleasure	-5.95	< .001	.055	.234	-0.90	.368	.001	.036
Affective slider: arousal	-3.46	.001	.019	.139	-1.79	.074	.005	.072
D-VAMS: happy-sad	-6.87	< .001	.072	.269	0.41	.681	.000	.017
D-VAMS: sleepy-alert	-4.73	< .001	.036	.189	-1.43	.154	.003	.058
SPANE: positive	-5.20	< .001	.042	.204	-0.41	.245	.005	.016
SPANE: negative	3.12	.002	.016	.126	-1.21	.227	.002	.049

Note: The choice intervention was the reference group

Analyses of the per-protocol population revealed that receiving the choice-based intervention not only significantly increased post-intervention affective slider arousal scores compared to the usual care group, $t(594) = -3.62$, $p < .001$, r = .147, but also significantly increased scores compared to the fixed-content group, $t(594) = -2.10$, $p = .036$, r = .086. There were no other differences in analyses between the per-protocol and the intention-to-treat populations.

6.6.1.4 Summary of Results

In line with the first hypothesis, there were significant differences between groups found for the primary outcome, as well as all five secondary mood-

related outcomes, indicating that both interventions were successful in improving positive mood, compared to usual care.

In terms of hypothesis two, the results indicate that the standard fixed-content intervention was equivalent to the choice-based intervention for all primary and secondary mood-related outcomes. This suggests that the standard fixed-content intervention was as effective as the choice-based intervention in improving positive mood on the day of vaccination in this population. It is worth noting that sensitivity analyses showed that in the per-protocol population, the choice-based intervention showed a significant increase in affective arousal compared to usual care whilst the standard intervention did not, however this was not reflected in the D-VAMS measure of arousal, in which both the standard and choice-based intervention groups showed significantly higher scores compared to the usual care group.

6.6.2 ***Aim 2: To assess whether there are differences in four-week antibody responses to the influenza vaccine between the standard fixed-content, choice-based, and usual care groups.***

6.6.2.1 Research question

2.1 Were there significant differences between the standard fixed content, choice and usual care groups in terms of four-week antibody response to each influenza vaccine strain?

6.6.2.2 Hypotheses

In line with research indicating an association between positive mood and vaccine response, and on the basis of the assumption that the choice-based intervention would result in significantly higher positive mood compared to the standard intervention, two hypotheses were made:

(i) Both the standard fixed-content and choice-based interventions would result in significantly higher post-vaccination antibody levels compared to the usual care group.

(ii) The choice-based intervention would also result in significantly higher post-vaccination antibody levels compared to the standard fixed-content intervention.

However, it is worth noting that the For-ME trial was powered for the previous aim, with the main focus of the study being the effects of the intervention on mood, thus analyses regarding vaccine response were more exploratory.

6.6.2.3 Analyses: Hypothesis 1

To address the first hypothesis, the two intervention groups were combined, and ANCOVAs were used to compare the effect of receiving any positive mood intervention, with receiving usual care on four-week antibody response.

Before the main analyses, a series of paired sample t-tests were carried out for each of the three vaccine strains to assess the change in antibody levels from baseline to four-weeks post-vaccination and establish whether vaccination resulted in the anticipated increase in antibody levels. Table *6.7*

shows that antibody levels for all vaccine strains significantly increased from pre- to post-vaccination in the overall study population. Effect sizes ranged from 0.91 to 1.16, indicating large effects.

Table 6.7: Paired samples t-test to assess change in pre- to post-vaccination antibody levels in each vaccine strain

	Mean (SD), pre scores	**Mean (SD), post scores**	**Mean Difference (SD)**	***p****	**Cohen's d***
A/Kansas (H3N2)	0.75 (0.33)	1.12 (0.48)	0.45 (0.45)	< .001	1.159
B/Maryland (B)	1.28 (0.52)	1.62 (0.53)	0.34 (0.38)	< .001	0.906
A/Brisbane (H1N1)	0.91 (0.35)	1.17 (0.41)	0.27 (0.30)	< .001	0.948

Note: Values are raw optical densities
* Comparisons are made on $\log_{10}$ transformations of the data

Following this, to address the first hypothesis, antibody levels were compared between both intervention groups combine, and usual care. Table 6.8 shows the mean antibody level values at pre- and four-weeks post-vaccination.

Table 6.8: Pre- and post-intervention antibody levels in the combined intervention and usual care groups for each antigen strain, mean (SD)

	Combined intervention			**Usual care**		
	Pre	**Post**	**Adj. Post***	**Pre**	**Post**	**Adj. Post***
A/Kansas (H3N2)	0.75 (0.33)	1.19 (0.47)	1.20 (0.02)	0.81 (0.38)	1.20 (0.53)	1.18 (0.04)
B/Maryland (B)	1.27 (0.52)	1.60 (0.52)	1.61 (0.02)	1.38 (0.53)	1.66 (0.56)	1.61 (0.03)
A/Brisbane (H1N1)	0.91 (0.34)	1.17 (0.41)	1.18 (0.01)	0.94 (0.37)	1.19 (0.42)	1.18 (0.03)

Note: Scores are raw optical densities
* Post-intervention scores adjusted for pre-intervention scores. Values are mean and standard error.

A series of ANCOVAs were then carried out to assess whether there were significant differences between either intervention group combined and the usual care group in terms of post-vaccination antibody levels. Pre-intervention

antibody levels were included as covariates. These analyses showed that there were no significant effects of receiving any intervention on post-vaccination antibody levels, controlling for baseline levels, for any of the three antigen strains (Table 6.9; A/Kansas: $F(583) = 0.53$, $p = .469$, partial $\eta^2 = .001$; B/Maryland: $F(581) = 0.05$, $p = .832$, partial $\eta^2 = .000$; A/Brisbane: $F(582) = 0.16$, $p = .689$, partial $\eta^2 = .000$).

Table 6.9: ANCOVA comparing post-intervention antibody levels between participants who received either positive mood intervention and those who received usual care

	df	***F***	***p***	**Partial η^2**
A/Kansas (H3N2)	583	0.53	.469	.001
B/Maryland (B)	581	0.05	.843	< .001
A/Brisbane (H1N1)	582	0.16	.689	< .001

Note: Analyses are based on $\log_{10}$ transformations of the data

6.6.2.4 Analyses: Hypothesis 2

To address hypothesis two, all three intervention groups were compared to each other, allowing comparisons between the two positive mood interventions. Table 6.10 shows the mean raw optical densities pre- and post-vaccination in the three intervention groups. This is also illustrated in Figure 6.3. These data demonstrate that as well as in the overall study population, antibody levels in each group increased from pre- to post-vaccination. For both the A/Kansas and A/Brisbane antigen strains, the standard intervention group had the highest post-intervention levels, whereas the choice group had the lowest levels for all three strains. When adjusted for pre-vaccination antibody levels, the standard intervention group had the highest levels for all three vaccine antigen strains.

A series of ANCOVAs were carried out comparing the three groups, with pre-vaccination antibody levels included as covariates, to assess whether these differences in post-vaccination antibody levels between groups were significant. Results of the ANCOVAs however, revealed that there was no significant effect of group on post-vaccination antibody levels, after controlling for the effect of baseline levels for any of the three antigen strains (Table *6.11*; A/Kansas: $F(2, 582) = 0.78$, $p = .460$, partial $\eta^2 = .003$; B/Maryland: $F(2,580) = 0.19$, $p = .827$, partial $\eta^2 = .001$; A/Brisbane: $F(2,581) = 0.70$, $p = .497$, partial $\eta^2 = .002$).

6.6.2.5 Summary of Results

The results of these analyses indicate that across the study population, antibody levels increased from pre- to post-vaccination, and there was no significant difference between either positive mood intervention or the usual care control group in terms of antibody response to influenza vaccination. Point estimates indicated that for all three vaccine strains, those who received the standard intervention had higher post-vaccination antibody levels (adjusted for pre-vaccination levels). However, the choice intervention group had lower post-vaccination antibody levels than the usual care condition for the A/Brisbane strain, and marginally higher post-vaccination antibody levels compared to usual care for the remaining two strains.

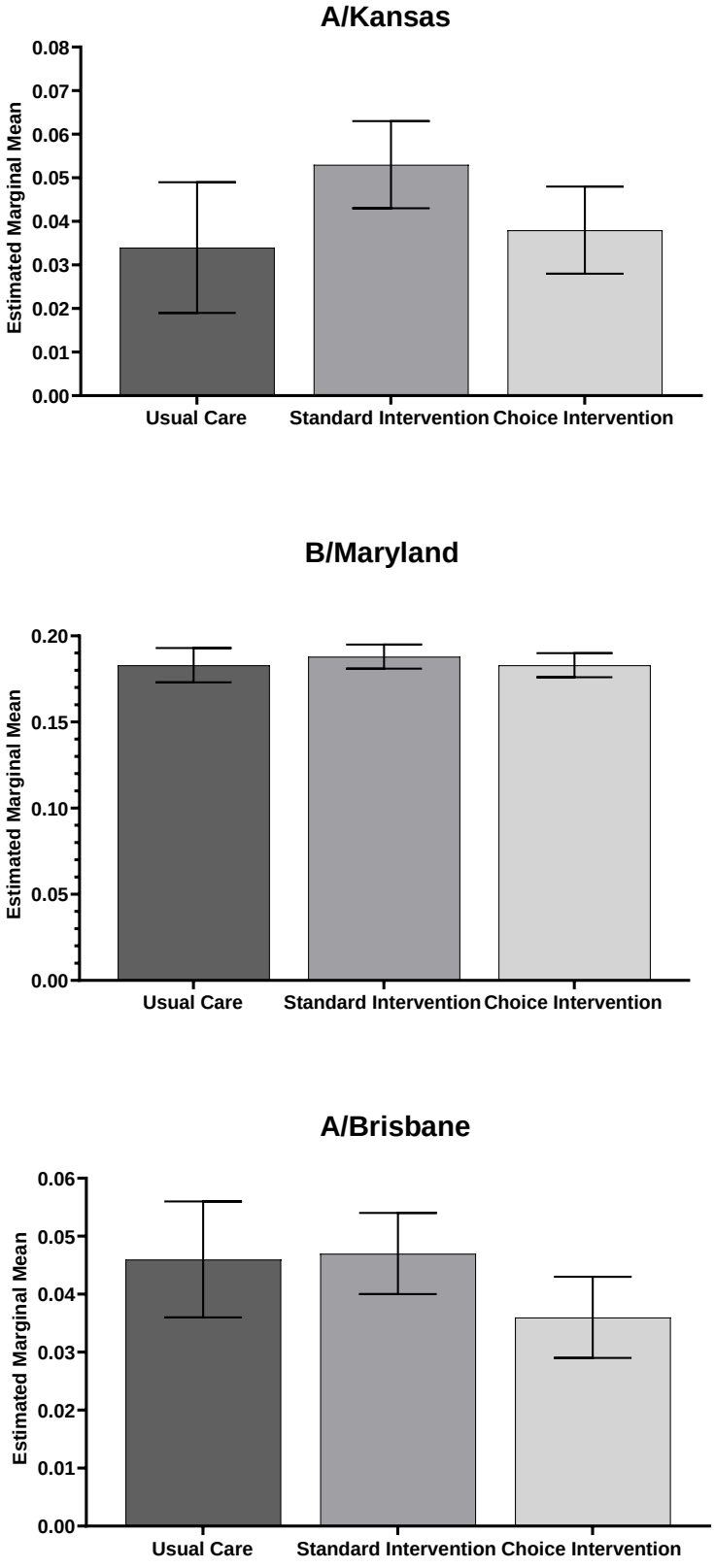


Figure 6.3: Antigen specific antibody responses to vaccination by group. Bars are $\log_{10}$ transformed means adjusted for pre-vaccination antibody levels by ANCOVA. Error bars are the standard error of the mean.

Table 6.10: Pre- and post-vaccination antibody levels according to group allocation for each antigen strain (mean, SD)

	Standard			Choice			Usual care		
	Pre	**Post**	**Adj. Post***	**Pre**	**Post**	**Adj. Post***	**Pre**	**Post**	**Adj. Post***
A/Kansas (H3N2)	0.76 (0.31)	1.22 (0.47)	1.23 (0.03)	0.75 (0.34)	1.16 (0.47)	1.17 (0.03)	0.81 (0.38)	1.20 (0.51)	1.18 (0.04)
B/Maryland (B)	1.28 (0.50)	1.63 (0.55)	1.64 (0.02)	1.26 (0.53)	1.58 (0.49)	1.60 (0.02)	1.38 (0.53)	1.66 (0.56)	1.61 (0.03)
A/Brisbane (H1N1)	0.90 (0.29)	1.19 (0.42)	1.20 (0.02)	0.91 (0.37)	1.15 (0.40)	1.15 (0.02)	0.94 (0.37)	1.19 (0.42)	1.18 (0.03)

Note: Scores are raw optical densities, mean (SD)

* Post-intervention scores adjusted for pre-intervention scores. Values are mean and standard error.

Table 6.11: ANCOVA comparing post-intervention antibody levels between participants who received the choice intervention, standard fixed contentment intervention, or usual care

	df	***F***	***p***	**Partial η^2**
A/Kansas (H3N2)	582	0.78	.460	.003
B/Maryland (B)	580	0.19	.827	.001
A/Brisbane (H1N1)	581	0.70	.497	.002

Note: Analyses are based on $\log_{10}$ transformations of the data

6.7 Chapter summary

This chapter has presented the findings of the main analyses of the For-ME trial, aiming to address the two study aims. These findings showed that both positive mood interventions significantly increased mood from pre- to post-intervention compared to usual care. However, despite this increase in positive mood, there were no significant differences between groups in terms of antibody response. The next chapter presents the results of exploratory analyses, aiming to examine these findings more closely and address some of the remaining questions regarding both the intervention and psychological influences on influenza vaccine response. An overall discussion of the evidence presented in both Chapters 6 and 7 will then be presented, including a summary of the findings, possible explanations for and implications of the findings, and some of the strengths and limitations of the study.

7 Chapter 7: The For-ME Study: Results from exploratory analyses

7.1 Chapter introduction

The previous chapter presented the results of the main analyses of the For-ME trial, showing that whilst positive mood significantly increased in both intervention groups compared to usual care, there were no significant differences between groups in terms of antibody response to vaccination. This chapter presents several exploratory analyses undertaken to try to examine and understand these findings, and address some of the outstanding questions. Firstly, the impact of trait affect and chronic psychological states on the primary outcome (state affect) will be explored to assess whether more stable measures influenced how participants responded to the interventions. The impact of these trait and chronic states on antibody levels will also be examined, to assess whether these more long-term measures may be better predictors of immune response compared to state affect measures. Secondly, the degree of change in state positive affect from pre- to post-intervention on antibody response will be explored, to assess whether the lack of significant findings may have been caused by individual differences in the response to the intervention that masked overall group effects. Finally, analyses exploring the effect of the relationship between positive and negative effect in terms of antibody response to vaccination will be presented, in an attempt to address a long-standing debate in research on affective states. Following this, the results of both the main analyses presented in Chapter 6 and the exploratory analyses presented here will be discussed in detail.

7.2 Results

7.2.1 *Trait and/or chronic states*

7.2.1.1 Research question

3.1 Did state affect change scores from pre- to post-intervention differ according to trait and/or chronic states?

7.2.1.2 Hypothesis

The previous chapter showed that both positive mood interventions resulted in significantly higher post-intervention state affect compared to the usual care group. However, it is unclear whether differences in trait affect or chronic states influenced how well individuals responded to the intervention. It may be expected that those with higher levels of trait negative mood and stress, and lower levels of trait positive affect would have larger improvements in state affect, given there is more room for improvement. Alternatively, for this group of individuals a brief positive mood intervention may not be sufficient to improve state affect. Thus, it was predicted that trait affects and chronic stress would be associated with change in state affect, however no prediction regarding the direction of the effect was made.

7.2.1.2.1 Analyses: approach 1

To investigate the relationship between trait and/or chronic states and change in state affect from pre- to post-intervention, several approaches to analyses are available. This section presents two such approaches. Firstly, a multiple linear regression was carried out to assess whether trait positive affect (PA), trait negative affect (NA), or chronic stress were predictive of response to the

intervention. To account for group allocation, dummy variables were created which were added to the first step of the model. The second step included adding the trait and/or chronic state measures to the model, including the PANAS (both positive and negative subscales) and the perceived stress scale. The dependent outcome was the change from pre- to post-intervention state positive affect, as measured by the affective slider pleasure subscale.

Results of the regression are presented in Table 7.1. Of the three measures, only chronic stress was found to be a significant predictor of change in state PA, with higher chronic stress scores associated with greater improvements in state PA (β = 0.400, $p < .001$).

Table 7.1: Multiple linear regression to assess the relationship between trait and chronic psychological factors and change in state PA from pre- to post-intervention

	B	**SE B**	**β**
Step 1			
Constant	2.688	1.244	
Standard intervention group	4.335	1.493	0.176*
Choice intervention group	4.687	1.483	0.191*
R^2	.017		
	$F(2, 525) = 5.465$, $p = .004$*		
Step 2			
Constant	-3.504	3.448	
Standard intervention group	4.110	1.409	0.167*
Choice intervention group	4.570	1.400	0.187*
PANAS positive	-0.060	0.074	-0.038
PANAS negative	0.244	0.127	0.113
PSS	0.400	0.108	0.231*
R^2	.0136		
ΔR^2	.116		
	$F(5, 520) = 16.398$, $p < .001$*		
	$\Delta F(3, 520) = 23.222$, $p < .001$*		

7.2.1.2.2 Analyses: approach 2

The second approach to explore the relationship between state affect and trait and/or chronic states was a tertiary split analysis, where scores on each measure were split according to those that scored in the lowest, middle and highest thirds. Table 7.2 and Figure 7.1 show the mean change scores for each third on the three measures.

Table 7.2: Change from pre- to post-intervention state PA between those scoring in the lowest, middle and highest thirds in pre-intervention state PA, trait PA and NA, and chronic stress (mean, SD)

	Lowest third	**Middle third**	**Highest third**
Trait PA	8.82 (15.32)	6.34 (12.02)	4.52 (8.42)
Trait NA	3.45 (7.60)	5.25 (10.26)	9.34 (14.76)
Chronic Stress	2.90 (7.69)	5.23 (9.44)	10.89 (15.85)

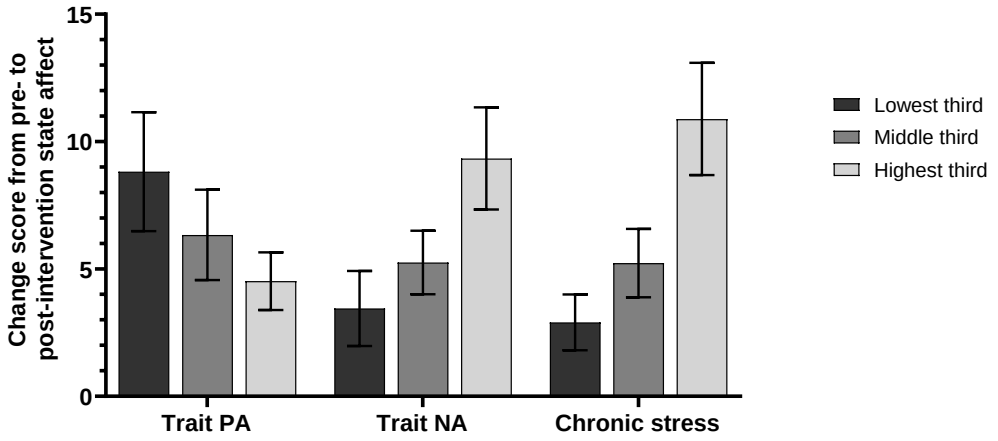


Figure 7.1: Change in pre- to post-intervention state affect according to the lowest, middle and highest scores in trait positive affect, trait negative affect and chronic stress. Error bars represent the confidence intervals

A series of Kruskal-Wallis tests were carried out to assess whether any differences between the lowest, middle and highest scoring participants on the trait and/or chronic measures in state affect were significant. Table 7.3 shows the results. There were significant differences between the thirds for all outcomes except for the state affect change score for the trait PA measure (p = .079). Dunn's pairwise tests were carried out to assess where these differences lay. The post-hoc tests showed that for trait NA and chronic stress, there was no significant difference between the lowest and middle group in change in state affect (p = .759 and .056, respectively), however the other two comparisons were significant for both measures (p < .05). Whilst there were no significant differences between the middle and highest groups, or the middle and lowest groups for the trait PA measure, the difference between the lowest and highest thirds was significant (p < .05).

Table 7.3: Kruskal-Wallis test with Dunn's pairwise post hoc tests to assess differences between those with the lowest, middle and highest trait PA, NA and chronic stress scores in terms of change from pre- to post-intervention state PA

	df	**H**	***p***	**Lowest vs. middle, *p***	**Lowest vs. highest, *p***	**Middle vs. highest, *p***
Trait PA	2	5.069	.079	1.000	.005	.077
Trait NA	2	16.834	< .001	.759	.001	.003
Chronic Stress	2	32.341	< .001	.056	< .001	.003

Note: Kruskal-Wallis test was performed due to violations in the assumption of homogeneity of variance

7.2.1.3 Summary of results

Results from the linear regression indicate that higher levels of chronic stress were associated with greater improvement in state affect following the intervention. Tertiary split analyses supported this, showing that there were

significant differences in the degree of improvement in state PA between those with the highest, middle and lowest stress scores. The tertiary split analyses also indicated that there was also a significant difference between the splits of trait NA in change scores. In terms of trait PA, only those with the lowest and highest scores were significantly different.

7.2.1.4 Research question

3.2 Did post-vaccination antibody levels differ according to trait and/or chronic states?

7.2.1.5 Hypotheses

The majority of the literature investigating the effect of psychological factors on vaccine effectiveness focuses on trait affect measures or chronic states such as stress. Indeed, high perceived stress and trait NA have been associated with reduced vaccine effectiveness (e.g. Marsland et al., 2001; Pedersen et al., 2009), whilst trait PA is associated with increased effectiveness (e.g. Marsland et al., 2006). Therefore, it was hypothesised that this relationship would be reproduced in the current study population, with higher levels of trait PA and lower levels of stress and trait NA associated with greater antibody response.

7.2.1.5.1 Analyses: approach 1

To address the hypothesis, firstly three multiple linear regressions were conducted, one for each vaccine antigen strain. Baseline adjusted post-vaccination antibody levels, using the Beyer method outlined in section 6.3.4 was the dependent variable, and the three trait and/or chronic state measures

were the primary predictor variables. Given that this exploratory analysis involved assessing the effects of trait and/or chronic states across the cohort, it was important to control for potentially confounding factors that have been shown to influence vaccine response, such as age (Pebody et al., 2017), BMI (Neidich et al., 2017; Sheridan et al., 2012), and physical health status (Gross et al., 1989; Sagawa, Kojimahara, Otsuka, Kimura, & Yamaguchi, 2011) that have previously been accounted for in analyses of between group effects by randomisation. Thus, age, BMI, and SF12 physical health were also included in the first step of the model as variables to be controlled for. As previously, group allocation was then added as the second step, and trait psychological measures as the third. Pearson's correlations showed that whilst several predictors were significantly correlated, there was no sign of multicollinearity (defined as r > .8; Field, 2009), indicating that inclusion of the predictors in the same model was appropriate.

Results of the linear regression can be seen in Table 7.4. None of the psychological measures were independent significant predictors of antibody response to vaccination the A/Kansas, B/Maryland or A/Brisbane antigens (trait PA: β = -0.076, *p* = .169; β = -0.032, *p* = .567; β = -0.076, *p* = .161; trait NA: β = -0.095, *p* = .174; β = 0.046, *p* = .511; β = 0.005, *p* = .937; chronic stress: β = 0.026, *p* = .727; β = -0.057, *p* = .444; β = 0.005, *p* = .947).

Table 7.4: Multiple linear regression to assess the relationship between trait and chronic psychological factors and response to vaccination

	A/Kansas			**B/Maryland**			**A/Brisbane**		
	B	**SE B**	**β**	**B**	**SE B**	**β**	**B**	**SE B**	**β**
Step 1									
Constant	0.470	0.141		0.340	0.091		0.373	0.098	
Age	-0.004	0.002	-0.131*	-0.002	0.001	-0.089	-0.003	0.001	-0.142*
BMI	0.000	0.002	0.012	0.000	0.001	0.018	0.001	0.001	0.041
SF12 physical health	-0.001	0.001	-0.066	-0.002	0.000	-0.169*	-0.001	0.001	-0.149*
R^2	.020			.035			.043		
	$F(3, 455) = 3.077$, $p = .027$*			$F(3, 454) = 5.495$, $p = .001$*			$F(3, 455) = 6.837$, $p < .001$*		
Step 2									
Constant	0.467	0.141		0.337	0.091		0.374	0.098	
Age	-0.004	0.002	-0.131*	-0.002	0.001	-0.089	-0.003	0.001	-0.142*
BMI	0.000	0.002	0.014	0.000	0.001	0.019	0.001	0.001	0.044
SF12 physical health	-0.001	0.001	-0.071	-0.002	0.000	-0.176*	-0.002	0.001	-0.154*
Standard intervention group	0.017	0.021	0.053	0.016	0.013	0.076	0.014	0.014	0.060
Choice intervention group	-0.007	0.021	-0.023	-0.005	0.013	-0.026	-0.012	0.014	-0.055
R^2	.025			.044			.054		
ΔR^2	.005			.009			.011		
	$F(5, 453) = 2.301$, $p = .044$*			$F(5, 452) = 4.176$, $p = .001$*			$F(5, 453) = 5.202$, $p < .001$*		
	$\Delta F(2, 453) = 1.134$, $p = .323$			$\Delta F(2, 452) = 2.155$, $p = .117$			$\Delta F(2, 453) = 2.676$, $p = .070$		
Step 3									
Constant	0.559	0.151		0.343	0.097		0.393	0.104	
Age	-0.005	0.002	-0.138*	-0.002	0.001	-0.085	-0.003	0.001	-0.137*
BMI	0.000	0.002	0.015	0.000	0.001	0.020	0.001	0.001	0.042
SF12 physical health	-0.001	0.001	-0.055	-0.002	0.001	-0.175*	-0.001	0.001	-0.129*
Standard intervention group	0.016	0.021	0.051	0.016	0.014	0.077	0.012	0.014	0.054

	A/Kansas			B/Maryland			A/Brisbane		
	B	**SE B**	**β**	**B**	**SE B**	**β**	**B**	**SE B**	**β**
Choice intervention group	-0.007	0.021	-0.022	-0.005	0.013	-0.024	-0.013	0.014	-0.058
PANAS positive	-0.002	0.001	-0.076	0.000	0.001	-0.032	-0.001	0.001	-0.076
PANAS negative	-0.003	0.002	-0.095	0.001	0.001	0.046	0.000	0.001	0.005
PSS	0.001	0.002	0.026	-0.001	0.001	-0.057	0.00007	0.001	0.005
R^2	.032			.046			.060		
ΔR^2	.008			.002			.006		
	$F(8, 450) = 1.887$, $p = .060$			$F(8, 449) = 2.702$, $p = .006$*			$F(8, 450) = 3.608$, $p < .001$*		
	$\Delta F(3, 450) = 1.192$, $p = .312$			$\Delta F(3, 449) = 0.280$, $p = .840$			$\Delta F(3, 450) = 0.953$, $p = .415$		

* $p < .05$

7.2.1.5.2 Analyses: approach 2

The second approach to assessing the impact of trait psychological factors on vaccine antibody response was to create a median split of each psychological outcome, categorising participants into those scoring highly, and those scoring low on each measure. Table 7.5 shows the mean baseline-adjusted post-intervention antibody levels for each psychological measure according to those in the lower median split and those in the higher split groups. This is also illustrated in Figure 7.2.

Table 7.5: Post-vaccination antibody levels for high and low scoring groups for each trait measure in the whole study population (mean, SD)

	Lower scores	Higher scores
A/Kansas (H3N2)		
PANAS: positive	1.25 (0.50)	1.14 (0.45)
PANAS: negative	1.18 (0.46)	1.22 (0.49)
PSS	1.19 (0.46)	1.21 (0.49)
B/Maryland (B)		
PANAS: positive	1.69 (0.55)	1.56 (0.51)
PANAS: negative	1.60 (0.53)	1.63 (0.53)
PSS	1.59 (0.51)	1.64 (0.55)
A/Brisbane (H1N1)		
PANAS: positive	1.23 (0.43)	1.12 (0.38)
PANAS: negative	1.14 (0.40)	1.20 (0.41)
PSS	1.16 (0.42)	1.19 (0.40)

Note: Values are raw optical densities.

A series of independent sample t-tests were then carried out to compare the low and high scoring groups for each measure. Table 7.6 shows the results of the t-tests. There were no significant differences between groups for the PANAS negative or PSS for any of the three antigen strains. However, there was a significant difference between low and high scoring participants in terms of trait positive affect, with those scoring higher on the PANAS positive scale showing significantly lower antibody levels in terms of all antigen strains (A/Kansas: $t(530) = 2.472$, $p = .014$, r = .107; B/Maryland: $t(529) = 2.452$, $p = .015$, r = .106; A/Brisbane: $t(529) = 3.585$, $p < .001$, r = .154).

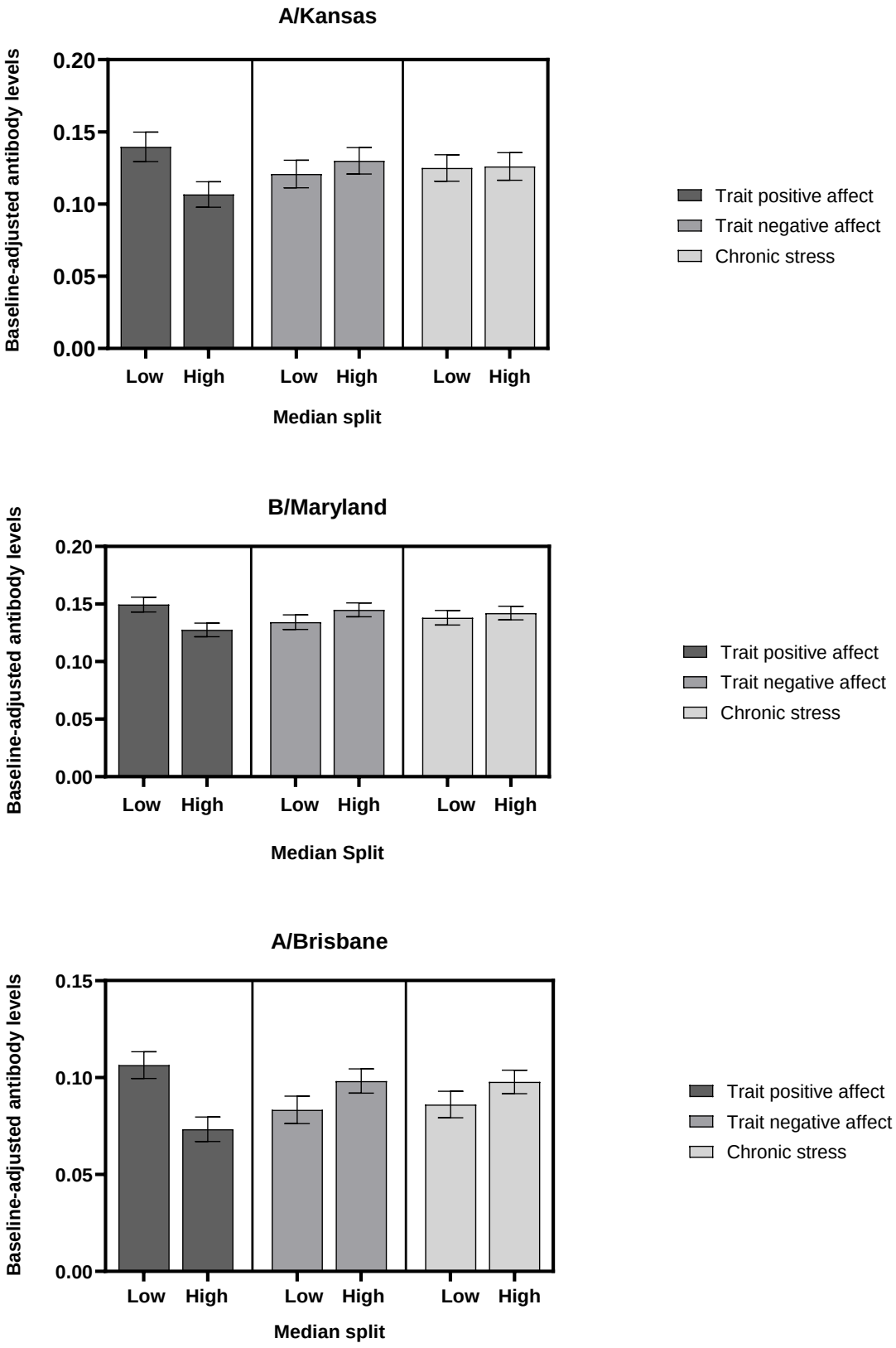


Figure 7.2: Antigen specific antibody response according to low or high scores in trait positive affect, trait negative affect and chronic stress according to a median split for each of the three vaccine antigens. Bars represent baseline-adjust post-vaccination $\log_{10}$ transformed antibody levels. Error bars are the standard error of the mean.

Table 7.6: Independent sample t-test to assess for differences between those with high and low scores on trait mood measure in terms of baseline-adjusted post-vaccination antibody levels in the whole study population

	df	*t*	*p*	r
A/Kansas (H3N2)				
PANAS: positive	530	2.472	.014	.107
PANAS: negative	545	-0.703	.482	.030
PSS	552	-0.081	.935	.003
B/Maryland (B)				
PANAS: positive	529	2.452	.015	.106
PANAS: negative	544	-1.210	.227	.052
PSS	551	-0.436	.663	.019
A/Brisbane (H1N1)				
PANAS: positive	529	3.585	< .001	.154
PANAS: negative	544	-1.559	.120	.067
PSS	551	-1.289	.198	.055

Note: Analyses are based on $\log_{10}$ transformed values

7.2.1.6 Summary of results

Results of the linear regressions showed that trait positive affect, trait negative affect and chronic perceived stress were not predictive of antibody response for any of the three antigen strains. Additionally, median split analyses demonstrated that there were no significant differences between those scoring highly and those with low scores in terms of vaccine response for both trait NA and stress. Whilst there was a significant difference between groups in terms of trait PA for all three antigen strains, the direction of the effect was in the opposing direction to what would be expected, with mean scores demonstrating that those with lower trait PA had higher levels of vaccine antibodies.

7.2.2 ***Change in state affect***

7.2.2.1 Research question

4.1 Is the degree to which participants' state positive affect changed related to antibody response?

7.2.2.2 Hypotheses

The previous chapter demonstrated that there were no significant differences between groups in any of the three antigen strains at post-vaccination, whilst controlling for the effect of pre-vaccination scores. One potential explanation of this is that individual differences between participants in the impact of the intervention on positive mood may have masked any overall group effects. Therefore, exploratory analyses were conducted to assess whether the size of the change in PA was related to antibody response to vaccination. It was expected that greater increases in PA would be associated with higher baseline-adjusted post-vaccination antibody levels.

7.2.2.2.1 Analyses: approach 1

To investigate the relationship between the change in state affect and vaccine response, firstly, a multiple linear regression was carried out, with baseline adjusted post-vaccination antibody levels as the dependent variable, and the primary outcome measure (affective slider: pleasure) as the independent variable. Given the exploratory nature of this analysis, the independent variable was operationalised in two additional ways: change from pre- to post-intervention, which was computed by subtracting post- scores from pre-scores and post-intervention scores only; and to account for possible ceiling effects on the affective slider, a single item question included at the end of the intervention. This question asked participants “compared to when we asked you these questions the first time, which of the options below best describe your mood right now”, with possible responses ranging on a scale of 1 to 5 from “a lot worse” to “a lot better”. As previously, potentially confounding

factors shown to influence vaccine response, including age, BMI and physical health status were controlled for (Gross et al., 1989; Neidich et al., 2017; Pebody et al., 2017; Sagawa et al., 2011; Sheridan et al., 2012). Thus, these measures were also included in the first step of the model as variables to be controlled for. Similarly, to account for group allocation, dummy variables were added to the second step of the model. The final step included the addition of each of the operationalisations of change in state PA, in three separate models.

Results of the multiple linear regressions can be found in Tables 7.7-9. Change in PA was not found to be an independent significant predictor of antibody response to vaccination for any of the three antigens, using any of the outcome operationalisations (change score: β = 0.005, *p* = .916; β = 0.059, *p* = .187; β = 0.083, *p* = .060; post-intervention score: β = 0.040, *p* = .380; β = 0.039, *p* = .385; β = 0.026, *p* = .560; single item mood question: β = -0.031, *p* = .497; β = 0.008, *p* = .858; β = 0.003, *p* = .951).

Table 7.7: Multiple linear regression to assess the relationship between change in state PA as measured by the Affective Slider: Pleasure (change score) and response to vaccination

	A/Kansas			**B/Maryland**			**A/Brisbane**		
	B	**SE B**	**β**	**B**	**SE B**	**β**	**B**	**SE B**	**β**
Step 1									
Constant	0.433	0.131		0.311	0.084		0.343	0.090	
Age	-0.004	0.001	-0.119*	-0.002	0.001	0-.079	-0.003	0.001	-0.130*
BMI	0.001	0.001	0.018	0.001	0.001	0.043	0.001	0.001	0.065
SF12 physical health	-0.001	0.001	-0.080	-0.002	0.000	-0.188*	-0.002	0.000	-0.179*
R^2	.019			.044			.055		
	$F(3, 494) = 3.162$, $p = .024$*			$F(3, 492) = 7.633$, $p < .000$*			$F(3, 494) = 9.514$, $p < .000$*		
Step 2									
Constant	0.425	0.132		0.304	0.084		0.342	0.090	
Age	- 0.004	0.001	-0.120*	-0.002	0.001	-0.079	-0.003	0.001	-0.132*
BMI	0.001	0.001	0.022	0.001	0.001	0.046	0.001	0.001	0.069
SF12 physical health	-0.001	0.001	-0.090	-0.002	0.000	-0.197*	-0.002	0.000	-0.186*
Standard intervention group	0.029	0.019	0.090	0.019	0.012	0.092	0.015	0.013	0.067
Choice intervention group	0.004	0.019	0.014	0.006	0.012	0.028	-0.004	0.013	-0.016
R^2	.025			.050			.061		
ΔR^2	.006			.006			.006		
	$F(5, 492) = 2.558$, $p = .027$*			$F(5, 490) = 5.163$, $p < .000$*			$F(5, 492) = 6.361$, $p < .000$*		
	$\Delta F(2, 492) = 1.639$, $p = .195$			$\Delta F(2, 490) = 1.438$, $p = .238$			$\Delta F(2, 492) = 1.597$, $p = .204$		
Step 3									
Constant	0.424	0.132		0.300	0.084		0.335	0.090	
Age	-0.004	0.001	-0.120*	-0.002	0.001	-0.079	-0.003	0.001	-0.131*
BMI	0.001	0.001	0.023	0.001	0.001	0.047	0.002	0.001	0.072
SF12 physical health	-0.001	0.001	-0.090	-0.002	0.000	-0.194*	-0.002	0.000	-0.181*

	A/Kansas			B/Maryland			A/Brisbane		
	B	**SE B**	**β**	**B**	**SE B**	**β**	**B**	**SE B**	**β**
Standard intervention group	0.028	0.020	0.089	0.016	0.013	0.079	0.011	0.014	0.049
Choice intervention group	0.004	0.020	0.013	0.003	0.013	0.014	-0.008	0.013	-0.035
Affective slider: pleasure (change score)	0.00006	0.001	0.005	0.000	0.000	0.059	0.001	0.000	0.083
R^2	.025			.053			.067		
ΔR^2	.000			.003			.007		
	$F(6, 491) = 2.129$, $p = .049$*			$F(6, 489) = 4.601$, $p < .000$*			$F(6, 491) = 5.920$, $p < .000$*		
	$\Delta F(1, 491) = 0.011$, $p = .916$			$\Delta F(1, 489) = 1.750$, $p = .187$			$\Delta F(1, 491) = 3.548$, $p = .060$		

* $p < .05$

Table 7.8: Multiple linear regression to assess the relationship between change in state PA as measured by the Affective Slider: Pleasure (post score) and response to vaccination

	A/Kansas			B/Maryland			A/Brisbane		
	B	**SE B**	**β**	**B**	**SE B**	**β**	**B**	**SE B**	**β**
Step 1									
Constant	0.450	0.131		0.312	0.083		0.348	0.089	
Age	-0.004	0.001	-0.122*	-0.002	0.001	-0.079	-0.003	0.001	-0.133*
BMI	0.000	0.001	0.013	0.001	0.001	0.043	0.001	0.001	0.067
SF12 physical health	-0.001	0.001	-0.085	-0.002	0.000	-0.190*	-0.002	0.000	-0.182*
R^2	.020			.045			.057		
	$F(3, 499) = 3.357$, $p = .019$*			$F(3, 497) = 7.893$, $p < .000$*			$F(3, 499) = 10.069$, $p < .000$*		
Step 2									
Constant	0.446	0.131		0.307	0.083		0.350	0.090	
Age	-0.004	0.001	-0.124	-0.002	0.001	0-.080	-0.003	0.001	-0.135*
BMI	0.001	0.001	0.017*	0.001	0.001	0.046	0.001	0.001	0.070
SF12 physical health	-0.001	0.001	-0.093	-0.002	0.000	-0.199*	-0.002	0.000	-0.188*
Standard intervention group	0.024	0.019	0.076	0.017	0.012	0.085	0.013	0.013	0.060
Choice intervention group	0.001	0.019	0.003	0.004	0.012	0.021	-0.005	0.013	-0.023
R^2	.025			.051			.063		
ΔR^2	.005			.005			.006		
	$F(5, 497) = 2.572$, $p = .026$*			$F(5, 495) = 5.283$, $p < .000$*			$F(5, 497) = 6.692$, $p < .000$*		
	$\Delta F(2, 497) = 1.387$, $p = .251$			$\Delta F(2, 495) = 1.351$, $p = .260$			$\Delta F(2, 497) = 1.592$, $p = .205$		
Step 3									
Constant	0.418	0.135		0.289	0.086		0.337	0.093	
Age	-0.004	0.001	-0.124*	-0.002	0.001	0-.080	-0.003	0.001	-0.136*
BMI	0.000	0.001	0.015	0.001	0.001	0.044	0.001	0.001	0.069

	A/Kansas			B/Maryland			A/Brisbane		
	B	**SE B**	**β**	**B**	**SE B**	**β**	**B**	**SE B**	**β**
SF12 physical health	-0.001	0.001	-0.097*	-0.002	0.000	-0.203*	-0.002	0.000	-0.191*
Standard intervention group	0.022	0.019	0.070	0.016	0.012	0.079	0.013	0.013	0.056
Choice intervention group	-0.002	0.020	-0.006	0.003	0.012	0.013	-0.006	0.013	-0.029
Affective slider: pleasure (post score)	0.000	0.000	0.040	0.000	0.000	0.039	0.000	0.000	0.026
R^2	.027			.052			.064		
ΔR^2	.002			.001			.001		
	$F(6, 496) = 2.272$, $p = .036$*			$F(6, 494) = 4.526$, $p < .000$*			$F(6, 496) = 5.626$, $p < .000$*		
	$\Delta F(1, 496) = 0.774$, $p = .380$			$\Delta F(1, 494) = 0.755$, $p = .385$			$\Delta F(1, 496) = 0.341$, $p = .560$		

* $p < .05$

Table 7.9: Multiple linear regression to assess the relationship between change in state PA as measured by mood after intervention scores and response to vaccination

	A/Kansas			**B/Maryland**			**A/Brisbane**		
	B	**SE B**	**β**	**B**	**SE B**	**β**	**B**	**SE B**	**β**
Step 1									
Constant	0.473	0.129		0.301	0.082		0.324	0.089	
Age	-0.004	0.001	-0.131*	-0.002	0.001	-0.075	-0.003	0.001	-0.122*
BMI	0.000	0.001	-0.004	0.001	0.001	0.028	0.001	0.001	0.053
SF12 physical health	-0.001	0.001	-0.071	-0.001	0.000	-0.162*	-0.002	0.000	-0.157*
R^2	0.019			0.033			0.043		
	$F(3, 508) = 3.277$, $p = .021$*			$F(3, 506) = 5.684$, $p = .001$*			$F(3, 508) = 7.638$, $p < .000$*		
Step 2									
Constant	0.471	0.130		0.297	0.083		0.327	0.089	
Age	-0.004	0.001	-0.132*	-0.002	0.001	-0.076	-0.003	0.001	-0.124*
BMI	-0.00004	0.001	-0.001	0.001	0.001	0.030	0.001	0.001	0.055
SF12 physical health	-0.001	0.001	-0.077	-0.002	0.000	-0.169*	-0.002	0.000	-0.161*
Standard intervention group	0.021	0.019	0.065	0.014	0.012	0.070	0.011	0.013	0.050
Choice intervention group	-0.004	0.019	-0.013	0.001	0.012	0.003	-0.008	0.013	-0.037
R^2	.025			.037			.049		
ΔR^2	.006			.005			.006		
	$F(5, 506) = 2.545$, $p = .027$*			$F(5, 504) = 3.892$, $p = .002$*			$F(5, 506) = 5.261$, $p < .000$*		
	$\Delta F(2, 506) = 1.437$, $p = .239$			$\Delta F(2, 504) = 1.197$, $p = .303$			$\Delta F(2, 506) = 1.666$, $p = .190$		
Step 3									
Constant	0.489	0.133		0.294	0.085		0.326	0.091	
Age	-0.004	0.001	-0.131*	-0.002	0.001	-0.076	-0.003	0.001	-0.124*
BMI	-0.00003	0.001	-0.001	0.001	0.001	0.030	0.001	0.001	0.055
SF12 physical health	-0.001	0.001	-0.079	-0.002	0.000	-0.169*	-0.002	0.000	-0.161*

	A/Kansas			B/Maryland			A/Brisbane		
	B	**SE B**	**β**	**B**	**SE B**	**β**	**B**	**SE B**	**β**
Standard intervention group	0.024	0.020	0.075	0.014	0.013	0.067	0.011	0.014	0.049
Choice intervention group	-0.001	0.020	-0.002	-0.00002	0.013	0.000	-0.008	0.014	-0.038
Mood after intervention	-0.006	0.009	-0.031	0.001	0.006	0.008	0.000	0.006	0.003
R^2	.025			.037			.049		
ΔR^2	.001			.000			.000		
	$F(6, 505) = 2.195$, $p = .042$*			$F(6, 503) = 3.2442$, $p = .004$*			$F(6, 505) = 4.376$, $p < .000$*		
	$\Delta F(1, 505) = 0.462$, $p = .497$			$\Delta F(1, 503) = 0.032$, $p = .858$			$\Delta F(1, 505) = 0.004$, $p = .951$		

* $p < .05$

7.2.2.2.2 Analyses: approach 2

Change score values ranged from -34 to 57, with a median of 4. Given that some participants reported a decrease in positive mood from pre- to post-intervention, whilst other reported an increase, the second analysis involved creating a tertiary split of the computed change in affective slider: pleasure outcome. This created a new categorical outcome of the change in the affective slider outcome with three groups, allowing a comparison to be made between those scoring between -34 and 0, representing negative or no change (i.e. a worsening of state mood), a middle third which included scores of between 1 and 7, representing minimal positive change, and the highest third which included scores of between 8 and 57, representing those with the most positive change. Antibody response to vaccination for each vaccine antigen was compared between the three groups. The means and standard deviations of baseline-adjusted antibody levels according to each tertiary split group can be found in Table 7.10. Means and standard errors are also illustrated in Figure 7.3.

Table 7.10: Post-vaccination antibody levels for those showing worse scores or no change, those with minimal change, and those with the most positive change for each vaccine antigen (mean, SD)

	Worse/no change	Minimal change	Improved
A/Kansas (H3N2)	1.222 (0.465)	1.217 (0.492)	1.153 (0.471)
B/Maryland (B)	1.637 (0.545)	1.601 (0.510)	1.607 (0.536)
A/Brisbane (H1N1)	1.191 (0.414)	1.154 (0.406)	1.165 (0.405)

Note: Values are raw optical densities

A series of one-way ANOVAs were then carried out to compare the three groups in terms of each of the three antigen strains, which also found no significant no significant differences between groups (Table 7.11; A/Kansas:

(2, 549) = .646, p = .524, ω^2 = -.001; B/Maryland: F(2, 547) = 1.081, p = .340, ω^2 = .000; A/Brisbane: F(2, 548) = 1.310, p = .271, ω^2 = .001).

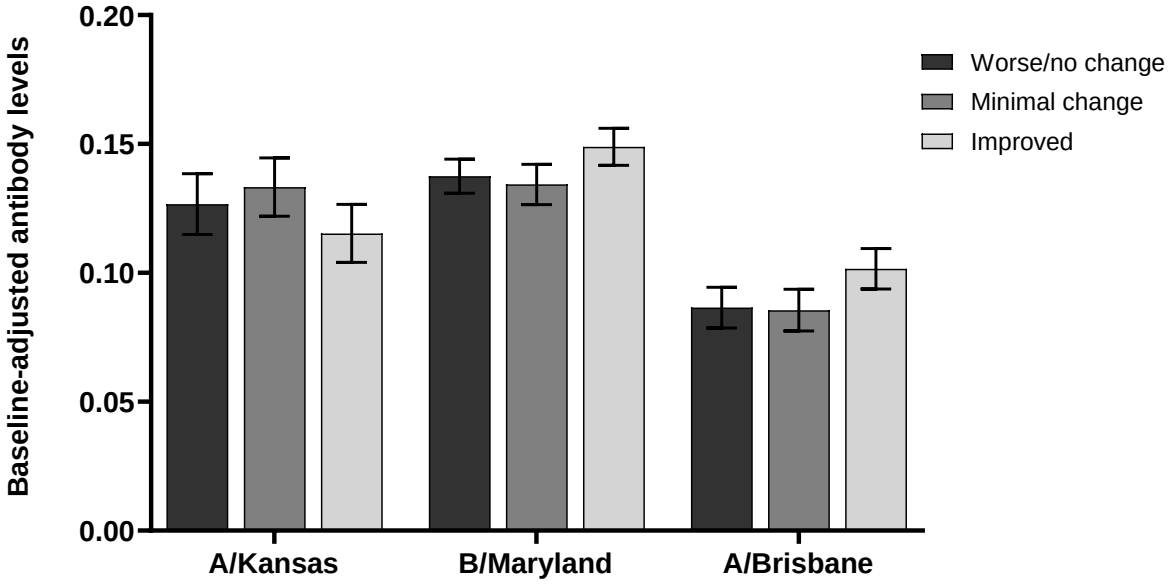


Figure 7.3: Antigen specific antibody response according to change in state mood according to a tertiary split. Bars represent baseline-adjust post-vaccination $\log_{10}$ transformed antibody levels. Error bars are the standard error of the mean.

Table 7.11: One-way ANOVA to assess for differences between those with worse/no change, minimal improvement and greater improvements in affective slider pleasure outcome in terms of baseline-adjusted post-vaccination antibody levels

	df	*F*	*p*	ω^2
A/Kansas (H3N2)	549	0.646	.524	-.001
B/Maryland (B)	547	1.081	.340	.000
A/Brisbane (H1N1)	548	1.310	.271	.001

Note: Analyses are based on $\log_{10}$ transformed values

7.2.2.3 Summary of results

Results of both the regression analyses and tertiary split analyses revealed that the degree of change in the primary outcome did not influence antibody

levels at four-weeks post-vaccination. Tertiary split analyses showed that there were no differences between those who either had decreased PA post-intervention, those who had minimal changes in PA, and those who had the greatest increases in PA, in terms of vaccine response, and regression analyses suggested that the degree of change in the primary outcome was not associated with post-vaccination antibody response. This goes against the hypothesis, which posited that those with greater increases in PA would have higher post-vaccination antibody response.

7.2.3 ***The relationship between positive and negative affect***

7.2.3.1 Research question

5.1 Did post-intervention state positive mood scores differ according to affective balance styles?

5.2 Did post-vaccination antibody levels differ according to affective balance styles?

7.2.3.2 Hypothesis

Chapter 2 briefly described a historical debate in the literature regarding the constructs of positive and negative affect, and there is not a clear view regarding the relationship between the two. To address this, a measure of affective balance was constructed, as described in Chapter 5 (section 5.6.6.1), in order to interrogate not only positive and negative affect as independent constructs, but the balance between the two. Analyses were conducted to explore the effect of different affective balance styles. Given the exploratory nature of the literature, hypotheses were two-directional:

(i) There would be significant differences between affective balance styles in terms of post-intervention state positive affect scores.

(ii) There would be significant differences between affective balance styles in terms of post-intervention antibody levels.

7.2.3.3 Analysis: Hypothesis 1

Four affective balance categories were created, based on those in Hassett et al. (2008), using PANAS population means, so that high PA was represented by scores over 31.3 on the PANAS positive subscale, and high NA was represented by scores over 16.0 on the PANAS negative subscale. The four groups included 'healthy' (high PA and low NA; n=325), 'low' (low PA, low NA; n=101), 'reactive' (high PA, high NA; n=73) and 'depressive' (low PA, high NA; n=74). The mean PA and NA scores in each of the affective balance style groups are displayed in Table 7.12.

Table 7.12: PANAS positive affect and PANAS negative affect scores in the four affective balance style groups (mean, SD)

	Healthy	**Low**	**Reactive**	**Depressive**
PANAS positive affect	38.89 (4.66)	26.19 (5.62)	37.42 (4.34)	25.28 (4.56)
PANAS negative affect	12.06 (1.82)	12.29 (1.92)	20.29 (4.04)	25.38 (5.81)

To assess whether there were any differences between the four affective balance styles in terms of the effect of the intervention on the primary positive state mood outcome, a one-way ANCOVA was conducted, with post-intervention scores as the independent variable, and pre-intervention scores as the covariate. The mean affective slider pleasure scores at pre- and post-

intervention, as well as change from pre- to post-intervention, in the four groups are presented in Table 7.13, Figure 7.4 and Figure 7.5.

Results of the ANCOVA showed that there was a significant effect of affective balance style on post-intervention scores after controlling for the effect of pre-intervention scores (Table 7.14; $F(3, 538) = 3.888$, $p < .05$, partial $\eta^2 = .021$). Post-hoc tests showed that there was a significant difference between the 'healthy' and 'low' ($p = .003$), as well as the 'low' and 'reactive' ($p = .002$) affective balance styles, with means showing that both the 'healthy' and 'reactive' groups had significantly higher scores on the affective slider: pleasure scale than the 'low' group. In terms of change scores, results of the ANOVA showed that there was also a significant effect of affective balance (Table 7.14; $F(3, 542) = 11.874$, $p < .001$, partial $\eta^2 = .062$). Post-hoc tests showed that there was a significant difference between the 'healthy' and 'reactive' ($p = .018$), 'healthy' and 'depressed' ($p < .001$), and 'low' and 'depressed' ($p = .001$) groups, with 'reactive' and 'depressed' groups showing the biggest change score compared to 'healthy' and 'low' groups.

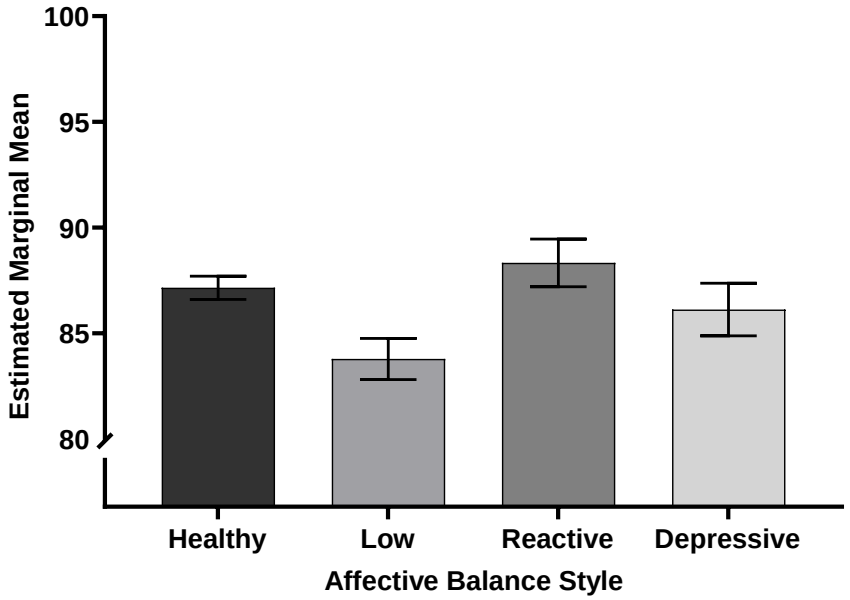


Figure 7.4: Affective slider: Pleasure subscale scores in the four affective balance style groups. Bars are mean values adjusted for baseline scores. Error bars are standard errors.

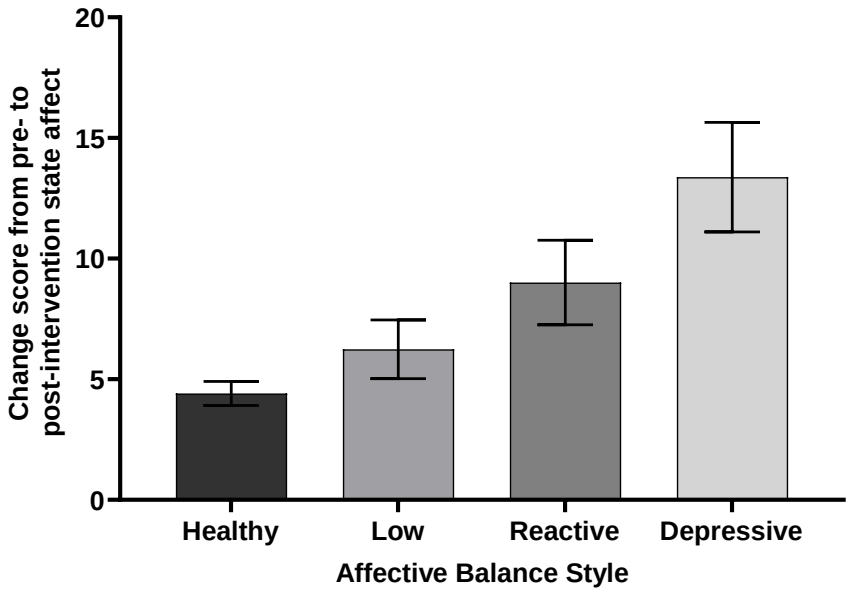


Figure 7.5: Affective slider: Pleasure subscale scores in the four affective balance style groups. Bars are change scores. Error bars are standard errors.

Table 7.13: Post-intervention scores according to the four affective balance styles on the primary outcome measure (mean, SD)

	Affective slider: pleasure
Healthy	
- **Pre**	86.34 (13.48)
- **Post**	90.76 (11.67)
- **Change score**	4.41 (8.89)
Low	
- **Pre**	73.68 (19.64)
- **Post**	79.91 (15.70)
- **Change score**	6.24 (11.91)
Reactive	
- **Pre**	77.34 (19.44)
- **Post**	87.01 (12.58)
- **Change score**	9.01 (14.50)
Depressive	
- **Pre**	61.69 (24.72)
- **Post**	75.64 (19.59)
- **Change score**	13.38 (12.00)

Table 7.14: ANCOVA and ANOVA to compare the four affective balance styles in terms of post-intervention (with pre-intervention score as the covariate) and change from pre- to post-intervention state positive affect

	df	***F***	***p***	**Partial η^2**
Affective slider: pleasure: final score	538	3.888	.009	.021
Affective slider: pleasure: change score	542	11.874	< .001	.062

7.2.3.4 Analysis: Hypothesis 2

To compare the affective balance styles in terms of the antibody outcome, a series of one-way ANCOVAs were conducted, with post-intervention $\log_{10}$ transformed antibody levels as the dependent variable and pre-intervention $\log_{10}$ transformed antibody levels included as the covariate. Pre- and post-intervention mean antibody levels for each antibody strain according to the four affective balance groups can be found in Table 7.15 and are illustrated in Figure 7.6.

Table 7.15: Pre- and post-intervention scores according to the four affective balance styles in terms of antibody levels for each antigen strain (mean, SD)

	A/Kansas	B/Maryland	A/Brisbane
Healthy			
- **Pre**	0.757 (0.310)	1.288 (0.513)	0.916 (0.335)
- **Post**	1.180 (0.466)	1.576 (0.506)	1.131 (0.369)
- **Adj. Post***	1.189 (0.026)	1.588 (0.021)	1.137 (0.017)
Low			
- **Pre**	0.778 (0.403)	1.360 (0.555)	0.938 (0.366)
- **Post**	1.222 (0.499)	1.667 (0.571)	1.204 (0.447)
- **Adj. Post***	1.123 (0.046)	1.616 (0.038)	1.180 (0.031)
Reactive			
- **Pre**	0.733 (0.350)	1.214 (0.502)	0.833 (0.295)
- **Post**	1.156 (0.447)	1.595 (0.506)	1.158 (0.416)
- **Adj. Post***	1.171 (0.053)	1.667 (0.044)	1.223 (0.036)
Depressive			
- **Pre**	0.798 (0.339)	1.364 (0.549)	0.959 (0.359)
- **Post**	1.287 (0.550)	1.769 (0.593)	1.312 (0.474)
- **Adj. Post***	1.245 (0.054)	1.714 (0.044)	1.252 (0.037)

Note: Scores are raw optical densities, mean (SD)
* Post-intervention scores adjusted for pre-intervention scores. Values are mean and standard error.

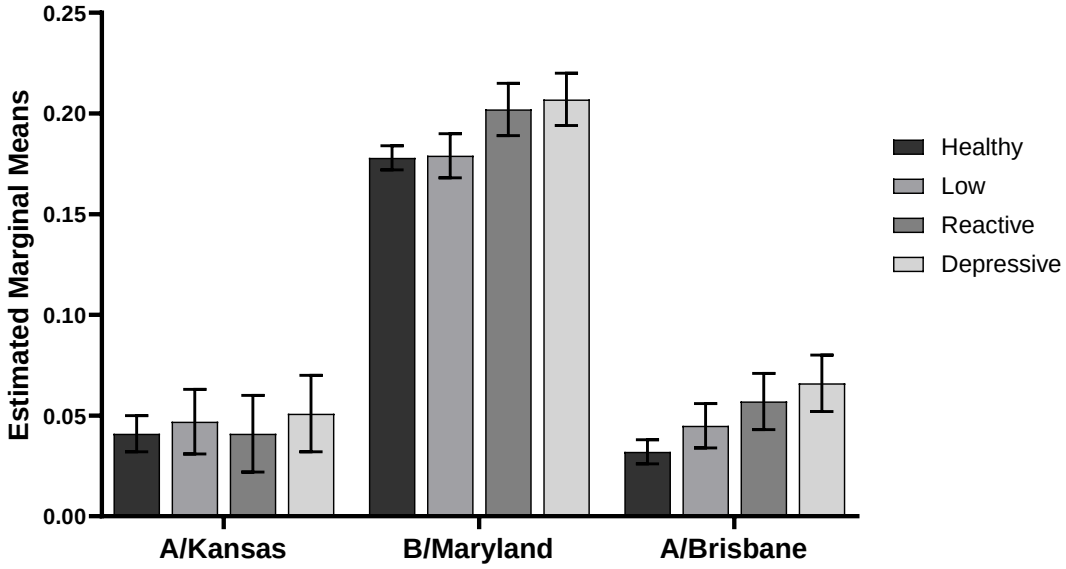


Figure 7.6: Antibody levels in the four affective balance style groups. Bars are log_{10} transformed means adjusted for pre-vaccination antibody levels by ANCOVA. Error bars are standard errors.

The ANCOVAs found no significant differences between the four affective balance states in terms of post-vaccination antibody levels, for any of the three antigen strains (Table 7.16; A/Kansas: $F(3, 509) = 0.108$, $p = .955$, partial $\eta^2 = .001$; B/Maryland: $F(3, 508) = 2.216$, $p = .085$, partial $\eta^2 = .013$; A/Brisbane: $F(3, 508) = 2.263$, $p = .080$, partial $\eta^2 = .013$).

Table 7.16: ANCOVA to compare the four affective balance styles in terms of the antibody levels for each of the three vaccine antigen strains at post-intervention

	df	***F***	***p***	**Partial η^2**
A/Kansas (H3N2)	508	0.103	.958	.001
B/Maryland (B)	507	2.212	.086	.013
A/Brisbane (H1N1)	507	2.283	.078	.013

Note: Analyses are based on $\log_{10}$ transformations of the data

7.2.3.5 Summary of results

Regarding hypothesis one, results showed that those with a 'low' affective balance style, with low scores on both the positive and negative subscales of the PANAS, had significantly lower post-intervention state positive affect scores according to the Affective slider: pleasure subscale, compared to both the healthy (high positive affect, low negative affect) and the reactive (high positive affect and high negative affect) affective balance styles. However, there were no significant differences between the healthy and reactive styles, nor were there any other significant differences found. These results did not extend to the antibody level outcomes, with no significant differences found between the four affective styles for any of the vaccine antigen strains. Thus, whilst there was some support for hypothesis one, hypothesis two was not supported.

7.3 Discussion

Chapters 6 and 7 presented the results of the For-ME trial, in relation to the effects of the interventions on mood outcomes and antibody response to vaccination. A recap of the main findings is given here, along with the implications of these findings, and a discussion of the strengths and limitations of the study.

7.3.1 ***Recap of findings and implications***

7.3.1.1 State mood

Standard fixed-content intervention versus usual care

The For-ME trial had two aims. The main aim of the For-ME study was to assess the impact of two brief interventions on mood on the day of influenza vaccination. This was to address two primary outstanding questions from the previous feasibility study. Firstly, whether the standard mood intervention significantly improved mood compared to usual care, as opposed to an active control group. The previous study involved a neutral mood comparator group, therefore it was unclear what the additional benefit of the intervention over standard practice might be. Given that the neutral mood intervention may have resulted in an attenuation of results as a consequence of being an active comparator, it would be expected that a comparison to usual care would result in greater between group differences. Indeed, results showed that compared with the usual care arm, those in the standard intervention group had significantly higher post-intervention scores on all of the six mood outcomes in the intention-to-treat population, indicating increased positive mood. However, when focusing on the affective slider only, which was common to both the present study and the Ayling et al., (2019) study, effect sizes were smaller in

the present study when comparing the standard intervention and control group (slider pleasure: partial η^2 = .066 vs .060; slider arousal: partial η^2 = .033 vs .009). Due to the increased sample size in the present study the smaller effect sizes are likely to be more accurate, however it is unclear why larger effect sizes were not found. One possible explanation is that the neutral mood intervention previously employed did not improve mood above what would normally be seen in usual care, or may have been poorer performing than usual care. An alternative explanation may be that the processes involved in the usual care arm were not reflective or representative of actual usual care. This is discussed further in section 7.3.3 as a potential limitation of the study.

Choice-based intervention versus standard intervention and usual care

The second outstanding question was concerned with whether the standard intervention could be optimised to further maximise the likelihood of seeing any potential benefits of mood improvement in terms of post-vaccination antibody response. As demonstrated by the results of the systematic review and meta-analyses in Chapter 4, choice-based interventions have several benefits, including increasing satisfaction and reducing drop-out. Whilst the effects of choice-based interventions on mood were mixed and limited by a small number of studies, they did suggest that further investigation to assess whether choice-based interventions was warranted. Results of the For-ME trial presented in Chapter 6 showed that both the standard and choice-based interventions resulted in significantly higher levels of positive mood. However, there were no significant differences between the standard and choice-based intervention for any positive mood outcomes. This suggests that the two interventions were equally effective in terms of enhancing positive mood in this older adult population, contrary to what may be expected. Indeed, this

goes against the hypothesis that choice may lead to increased positive mood by increasing autonomy and perceived control, which are associated with positive mood, as outlined in Chapter 4 (Dan-Cohen, 1992; Grob, 2000; Reis et al., 2000; Rotter, 1966; Sheldon et al., 1996; Staub, 2013).

One potential explanation as to why the choice intervention did not enhance positive mood beyond that of the standard intervention is that the intervention content alone was sufficient in enhancing mood. This may have resulted in any potential additional benefits of participant choice being masked or 'swamped' by the effects of the intervention content. Alternatively, it may be that in conditions where the intervention content is sufficiently adequate, the presence or absence of choice is unimportant. Indeed, previous researchers have concluded that the importance of perceived control, which is associated with choice, drops as satisfaction increases (Leaman & Bordass, 1999). This suggests that choice in this context is unnecessary, and the standard intervention is sufficiently optimised as is. An alternative explanation may be that participants do not necessarily choose content that they would improve their mood the most, but rather make selections based on familiarity for example, which may not necessarily translate to better enjoyment. Indeed, in a study that found no differences between those who could select one of four positive interventions and those with no choice, Silberman (2007) concluded that participants were unable to determine which intervention they would derive the greatest benefit from. Other methods of intervention selection, such as the use of a skilled coach as suggested by Silberman, or using individualisation based on assessments of what participants enjoy more broadly, may therefore result in greater mood increases. Finally, it is possible that for some participants, choice may be stressful – too many good options to

choose from may lead to feelings of missing out, being overwhelmed or cognitive overload, leading to feelings of regret (Iyengar & Lepper, 2000; Iyengar, Wells, & Schwartz, 2006), whereas too few appropriate options may lead to frustration. Therefore, any potential benefits of choice may be offset by these negative reactions when available choice options are not ideal for the individual. It is also worth considering that participants in the choice group in the present study were not aware that those in the standard group did not receive choice. Whilst there is evidence that knowledge of restricted or denied choice may have negative consequences (e.g. Bradley, 1993; Deci, Connell, & Ryan, 1975; Feine et al, 1998), it is unclear what the effect of knowledge of increased choice over study counterparts may be. Indeed, it is plausible that this may have positive consequences due to an increased sense of personal responsibility, or simply as a result of making the presence of choice salient, rather than just being an integrated part of the intervention.

It is interesting to note that in the per-protocol analyses, the slider arousal outcome showed no significant difference between the standard intervention and usual care groups, and was the only outcome where there were significant differences between the two positive mood interventions. Whilst this finding may be the result of chance, an alternative explanation may be that providing participants with choice enhances affective arousal more than no-choice interventions. This is consistent with literature suggesting that choice may increase motivation (Cordova & Lepper, 1996; Swann Jr & Pittman, 1977), which may in turn be associated with increased arousal and alertness (Bradley & Lang, 2007). Alternatively, it may be a consequence of the choice intervention requiring a greater level of participant interaction, with participants required to select a video to watch every five minutes, compared to the

standard intervention in which participants are passive for the full 15 minutes. However, this finding was not repeated for the D-VAMS arousal measure, nor was it found in the intention-to-treat population.

Overall, by addressing these two outstanding questions, the For-ME study has demonstrated that both positive mood interventions were successful at significantly improving positive mood compared to usual care in the context of a busy vaccine roll-out programme, in a population of older adults with already high levels of positive mood, as indicated by high baseline scores. The lack of significant differences between the two interventions indicates that the way in which the intervention is operationalised, in terms of choice or fixed-content, did not matter, as both were equally effective. There remain many avenues to explore, and directions to take the intervention in the future. For instance, there are additional contexts both in and outside of primary care in which positive mood induction may have benefits. For instance, given the association between positive mood and increased pain threshold (Weisenberg, Raz, & Hener, 1998), there may be benefits before minor medical procedures such as biopsies. Additionally, rather than alternative brief medical encounters that may benefit from prior mood enhancement, there are also other populations with compromised immunity, such as those with HIV for instance, who may benefit from a positive mood induction prior to vaccination. Finally, whilst choice was employed as the strategy to optimise the standard fixed-choice intervention in the present study, other methods of optimisation are available and may be more effective than choice. These considerations are discussed in more detail in Chapter 9.

Influence of trait affect on state affect

To gain further insight into factors that may have influenced how well the intervention worked in terms of its primary outcome, positive mood, exploratory analyses were conducted to assess whether trait affects or chronic stress were associated with intervention response. Regression analysis showed that only chronic stress, and not trait positive or trait negative affect, was a significant predictor of intervention response, with higher stress levels associated with a greater increase from pre- to post-intervention positive mood. On the other hand, tertiary split analyses, in which those scoring in the bottom, middle and highest thirds on measures of trait positive affect, negative affect and chronic stress were compared to each other in terms of state affect, showed that for all three measures, there were significant differences in state affect change scores between the bottom and highest scoring groups. Additionally, for trait negative affect and chronic stress, the difference between the middle and highest scoring groups was also significant. Together, this suggests that those with greater levels of chronic stress, and potentially trait negative affect, are more likely to benefit from a 15-minute positive mood intervention. Only those with the lowest levels of trait positive affect are likely to have a benefit compared to those with moderate or high levels. This suggests trait and/or chronic states are influential in terms of response to a brief positive mood intervention, and that the interventions work best in those with higher levels of stress and negative affect, who may have more room for mood improvement.

7.3.1.2 Antibody response to vaccination

The second aim was to assess whether there were any differences between the three groups in terms of antibody response to influenza vaccination. The results showed that whilst antibody levels did significantly improve from pre- to post-vaccination across the study population and in each intervention group, there were no significant differences between groups for all three vaccine strains. These results therefore suggest that neither fixed-content or choice-based brief psychological interventions, delivered immediately prior to vaccination, were able to improve vaccine response in the older adult population compared to usual care. Given that the analysis of mood data demonstrated that both interventions were effective in significantly improving mood, the potential reasons as to why this did not translate to differences in antibody response need to be examined.

Statistical power

The study was powered based on the primary outcome (i.e. the affective slider: pleasure subscale), and powered to reliably detect moderate to large effect sizes. However, the results of the feasibility study showed very small effect sizes (partial η^2 = .001 - .007) for ANCOVAs comparing antibody levels at four-weeks post-vaccination between groups, therefore it was expected that effect sizes for antibody level outcome would be much smaller and the likelihood of not having sufficient power is high. A larger study that is sufficiently powered to detect changes in antibody levels may therefore be necessary to establish whether an effect can be detected, which would establish more conclusive results. Given the effect sizes seen in the present trial, it is expected that the sample size needed to detect a difference between

the intervention and usual care groups in terms of the antigen strain with the largest effect size (A/Kansas H3N2) with 80% statistical power would be 1957, based on the comparison of the standard fixed-content intervention and usual care groups. This estimate increases to 7843 participants when based on the comparison of effects averaged across all three groups.

Notwithstanding the issue of power, there are further considerations that should be discussed in terms of the null findings for the effect of the interventions on antibody responses. These include factors relating to the effects of the interventions on the immune system, such as the specific immune parameters affected, the duration of the intervention, how long any immune changes are sustained for and when the optimal window for vaccination is, as well as considerations regarding the degree of change in state positive affect, the role of trait affect, and the difference between statistical and clinical significance. Each of these will now be discussed in turn.

Positive mood intervention and immune system mechanisms

It is worth considering the immune outcome that was used as a marker of vaccine response: vaccine specific antibody levels. As noted in Chapter 1, antibody production is one of the final stages of a cascade of immune responses to occur following exposure to a pathogen or vaccine antigen, with many other immune parameters involved along the way. Very little is currently known regarding the specific mechanisms and pathways through which state affect might influence vaccine response, however it is possible that one or more other parameters are being affected in some way by the mood

interventions, that may also confer protection. For instance, previous research has found that older adults with higher levels of mood disturbance and fatigue were more likely to have poorer cytokine response to influenza vaccination (Costanzo et al., 2004), suggesting that helper T cells may be involved in the relationship between mood and vaccine response. Indeed, as mentioned in Chapter 3, cell-mediated measures of vaccine response (such as T cells, cytokines and macrophages) may in fact be better predictors of vaccine protection in older adults, rather than antibody levels (McElhaney et al., 2006). Therefore, whilst the For-ME study did not find any detectable effects of the interventions on antibody responses, it did not investigate intervention effects on these other immune parameters. A potential next step of this research may be to conduct some mechanistic studies to determine what, if any, alternative immune parameters are altered in response to changes in positive mood. The identification of these will lead to a better understanding of the pathways involved, and may potentially aid the understanding and development of more effective interventions.

Another consideration is that the duration of the intervention and its effects may not have been sufficient to enact meaningful immunological changes. Indeed, the 15-minute duration was based on a compromise between the pragmatics, informed by Public and Patient Involvement and discussion with GP practices regarding what would be practical in a primary care setting, and evidence of intervention lengths that may impact on various immune parameters. For instance, in a systematic review of brief single-session interventions aiming to improve mood as a means to enhance immune function, the duration of interventions varied widely, ranging from 90 seconds to 120 minutes, with the majority longer than 15 minutes (mean 48 minutes;

Ayling, Sungar & Vedhara, 2020). This suggests that consensus regarding the optimal duration of such interventions has not been reached, but that up to now longer interventions have been favoured. Longer interventions have indeed been associated with a range of immunological changes (Berk et al., 2001; Lefcourt, Davidson-Katz, & Kueneman, 1990; Mittwoch-Jaffe et al., 1995; Pawlow & Jones, 2005), however, the effect on vaccine specific immune response is unclear. There is a rationale supporting the notion that longer interventions may be more effective. For instance, as noted in Chapter 2, the HPA axis is a relatively slow responding system (Murison, 2016). Therefore, it may be that an intervention aiming to initiate immune changes need to last for a long enough duration to provoke responses in the parameters associated with this axis. Future work could examine whether a longer positive mood intervention may result in significant between group differences in antibody response to vaccination, however there are considerable pragmatic issues associated with this. For instance, longer interventions would have implications for the number of participants that could be seen in a single morning session, which may affect recruitment, would certainly have financial implications, and are unlikely to be practical in a primary care setting. Thus, longer interventions may necessitate alternative locations, such as at home interventions. However, such interventions also raise several issues, including intervention fidelity, given that the delivery of the intervention would not be supervised. Additionally, intervention timing in relation to vaccination may also be problematic, given that immediate vaccination would not be possible. This is discussed further in the next two paragraphs.

It is unclear how long mood enhancement needs to be sustained once the intervention is complete to see beneficial effects on the immune system or meaningful differences to antibody responses specifically. Following exposure to the intervention in the present study, participants were required to fill in post-intervention questionnaires before potentially waiting for a short period of time until they could receive their vaccination. Whilst this time delay was minimised as much as possible, it was often unavoidable due to various practical issues. This may have resulted in the effects of the intervention on mood 'wearing off' by the time of vaccination. Whilst some studies have found that immune changes resulting from mood induction, including increases in IgG and some leukocytes and lymphocytes, are sustained for as long as 12 hours following exposure (e.g. Berk et al., 2001), it is unclear if this is the case for vaccine specific immune responses.

Relatedly, it is unclear whether the timing of vaccination relative to the intervention is the optimal for enhanced immune response. For instance, in the case of stress, research has suggested that exposure before vaccination was not associated with antibody response, whereas exposure during the 10 days following vaccination was (Miller et al., 2004). Whilst it is unclear whether this translates to mood, similar pathways regarding the relationship between these constructs and the immune system have been proposed (e.g. Marsland et al., 2007; Pressman & Cohen, 2005). Therefore, it is possible that the period after vaccination may be of importance in the relationship between affect and vaccination response. Together, these considerations regarding timing and duration support future work benefiting from focusing on the potential mechanisms underlying the relationship between state positive affect and vaccine response. A better understanding of the specific immune

parameters involved in vaccine response that change during a 15-minute mood-enhancing intervention, how long the intervention should be, how long intervention-induced changes last, and the optimal timing of mood induction relative to vaccination, will allow for better informed judgements regarding the operationalisation of the intervention, potentially resulting in a more effective intervention.

Trait affect

A further point of consideration is the role of state as compared to trait affect. The results of this study suggest that state affect immediately prior to vaccination may not be related to vaccine response. Indeed, the previous literature suggesting a link between affect and vaccine response mainly focuses on trait, rather than state, affect, or other closely related constructs such as optimism. This literature has demonstrated associations between increased trait positive affect and improved vaccine specific antibody response (Ayling et al., 2019; Ayling, Fairclough, et al., 2018; Marsland et al., 2006), as well as poorer vaccine response associated with high trait negative affect (Marsland et al., 2001). This suggests that trait affect may be a better predictor of response to vaccination than state affect. However, exploratory analyses conducted to explore the relationship between trait measures and four-week post-vaccination antibody levels did not find a significant relationship between trait positive affect, trait negative affect, or chronic stress. On the basis of these null findings, a path analysis to assess whether trait measures influenced antibody level via effects on state positive mood was not carried out. Median split analyses suggested that, contrary to what was expected, those with lower levels of trait positive affect had higher post-vaccination antibody levels for one of the vaccine strains (H1N1), compared to

those with higher trait positive affect. No other significant differences between groups were noted.

It is unclear why previous findings regarding trait affect and stress were not replicated here. Regarding the Marsland studies, it is important to note that these were carried out in a younger population of healthy students who were receiving the hepatitis B vaccines, thus it may be that the association between affect and vaccine response is population and/or vaccine specific. For instance, results may be influenced by differences in immune functioning between populations, differences in how various adjuvanted and non-adjuvanted vaccines work, or by differences in prior exposure to the virus.

When considering previous studies with a similar population and vaccine, a potential explanation of the differences in the associations seen in the present study may relate to the vaccine itself. For instance, the 2019-2020 influenza vaccine was adjuvanted, which has not been the case in previously studied vaccination seasons. Adjuvanted vaccines are developed to be more effective at inducing a stronger immune response, eliciting higher antibody responses (Frey et al., 2014; Nicholson et al., 2001), and have been shown to be more effective in terms of reducing hospitalisations, deaths, and cardio-respiratory events (Lapi et al., 2019; Pellegrini, Nicolay, Lindert, Groth, & Della Cioppa, 2009; Pelton et al., 2020). As such, there may have been minimal opportunity for the additional benefit of psychological factors, including trait affect, to be observed. In other words, this relationship may only be observed when vaccine effectiveness is low, however when it reaches a certain level of effectiveness, the relationship is obscured. Therefore, this may also account

for why state affect was previously observed as associated with vaccine response (Ayling et al., 2018), but not in the present study.

Baseline mood and the degree of change

An alternative potential explanation for the lack of significant effects of either intervention on immunological outcomes may be that the participants had sufficiently high levels of positive mood at baseline, as indicated by the high pre-intervention positive affect scores. Thus, whilst mood did significantly improve in the two intervention arms, a ceiling effect may have resulted in these improvements not being big enough to translate to benefits in immunological outcomes. To investigate this possibility, exploratory analyses examined the relationship between the degree of change in mood and antibody levels, with the hypothesis that those with the biggest increase in mood from pre- to post-intervention (i.e., the biggest improvement) would have the highest post-vaccination antibody levels. However, these analyses found no significant relationship between the degree of change in post-intervention mood and antibody response to vaccination, and no difference between those with the biggest improvement in mood and those with either minimal change or decrease in mood. This suggests that within this population, larger increases in positive mood were not associated with better outcomes, although this may be confounded by the fact that only those with lower baseline scores had much scope to increase by a large amount. Thus, there was either no effect of enhanced mood on antibody response, or alternatively, even those with the greatest improvements in mood still scored too highly in baseline positive mood to result in an improvement big enough to see a significant impact on immune outcomes. Therefore, in the future it may be worth exploring the impact of state mood improvement in a targeted

population of those with a lower positive mood baseline scores compared to the current population, for instance those suffering from low mood or depression specifically, who therefore have greater opportunity to improve mood, and improve mood to a higher degree. Alternatively, it may be that there was sufficient room to improve, however the improvements seen in positive mood, whilst statistically significant, were not big enough to translate to meaningful changes to antibody response. This suggests either that both interventions could benefit from further optimisation in order to potentially create larger improvements in mood, or that other means of mood improvement may be more beneficial. Indeed, multiple session mood induction, music, relaxation and reflecting on autobiographical experiences have all been associated with changes to various non-specific immune parameters (Futterman et al., 1994; Hucklebridge et al., 2000; Knapp et al., 1992; McCraty et al., 1996; Rider et al., 1990), although the effect on vaccine specific antibody levels is unclear.

Statistical and clinical significance

Finally, it is worth reflecting on the difference between statistical and clinical significance. A disadvantage of using antibody levels as the primary measure of vaccine effectiveness is that it is unclear how this translates to clinical significance, that is, clinically meaningful outcomes for the patient, such as reduced illness, hospitalisation, pharmacy use etc. Indeed, as previously outlined by Ayling et al., (2019), given the low cost associated with the intervention and the high number of people receiving the vaccine each year, even modest improvements to vaccine response may prove to be cost-effective for both the health service and individual patient. This is evidenced in other low cost and high volume public health interventions, such as the use of

statins to prevent cardiovascular disease and events, which is one of the most commonly prescribed drugs in the UK (Curtis & Goldacre, 2018; NHS Digital, 2018c), despite small effect sizes (d = 0.15; Leucht, Helfer, Gartlehner, & Davis, 2015). Thus, whilst differences between groups in post-vaccination antibody levels were not statistically significant and effect sizes were very small, it is unclear whether this also means that these were not clinically significant. To assess this, as well as conducting sufficiently powered trials with antibody levels as the primary outcome, other measures of vaccine effectiveness, such as laboratory confirmed illness, doctor visits, hospitalisation, and use of over-the-counter medications, for example, should be considered for inclusion in future research. Not only will this help to determine whether either intervention results in clinically meaningful benefits, but it may also aid the understanding of the levels of post-vaccination antibodies that are associated with clinically relevant outcomes.

7.3.2 *The relationship between positive and negative affect*

As outlined in Chapter 2, there is some debate within the literature regarding the relationship between positive and negative affect. Whilst some argue that the two sit at either end of the same construct, others have proposed that positive and negative affect are in fact distinct, albeit highly correlated constructs. Indeed, the finding that negative affect is correlated with both anxiety and depression whilst positive affect is only correlated with depression (Watson, Clark, & Carey, 1988) provides support to the latter argument. However, the specific relationship between the two remains unclear, as does the relative importance of the two constructs in terms of health outcomes.

Whilst many studies of positive affect attempt to account for this relationship by including a measure of negative affect in the same model as a covariate, this can be problematic due to the often high correlation between the two measures (Diener & Emmons, 1984; Pressman et al., 2019). An alternative approach is the creation of categories based on affective balance, that is, relative levels of positive and negative affect (Hassett et al., 2008). Affective balance has been measured in several ways, including the Bradburn Affective Balance Scale (Bradburn, 1969) and the Balanced States of Mind Model (Schwartz & Caramoni, 1989), however both have been criticised for using outdated language and being overly simplistic (Kim & Mueller, 2001; MacIntosh, 1998). Here, the approach adopted by Hassett et al., (2008) was used, in which four distinct affect balance styles were created according to relative levels of positive and negative affect (see Section 5.6.6.1 for more details). This approach provides information regarding whether the degree of positive compared to negative affect influences outcomes, and thus gives insight into the relationship between these constructs.

Results of the affective balance analysis regarding the effects of the intervention on state positive affect showed that those with a 'reactive', followed by a 'healthy' affective balance as assessed by trait measures, had the highest baseline-adjusted post-intervention state positive affect scores, whereas those with 'depressed' followed by 'reactive' affective balance styles had the biggest mood improvement in positive affect. This suggests that those with high levels of negative affect, regardless of the level of positive affect, are more likely to see benefits from the intervention, despite post-intervention scores not being as high as those with high levels of positive affect. Those with both low positive and low negative trait affect had the lowest post-intervention state positive affect scores, and the second lowest improvement

from pre- to post-intervention, suggesting that this style is not conducive to benefiting from the intervention. It may be that the specific mix of low positive and low negative affect results in a 'mellow' disposition, where those with this affective balance style are less likely to experience emotional highs or lows (Hassett et al., 2008), thus less likely to have larger increases in state positive affect.

In terms of antibody outcomes, there were no significant differences between the four affective balance styles for any of the vaccine antigen strains. This may suggest that affective balance style does not impact on antibody response to vaccination, however these results may also reflect the issues previously discussed, regarding a potential lack of statistical power and the limitations of antibody levels as a measure of vaccine response. Indeed, in their study of affect balance styles in fibromyalgia and control patients, Hassett et al. (2008) suggests that the stress pathway (outlined in section 2.2.2) may be the link between affective balance and health, with depressive and reactive patients more likely to experience greater and more persistent activation of the stress response system. Thus, it may be expected that in an adequately powered trial with an appropriate measure of vaccine response, those with depressive or reactive affective balance styles exhibit poorer responses to vaccination.

7.3.3 *Strengths and limitations*

The For-ME study was the largest randomised controlled trial of its kind in the area of positive mood interventions and response to influenza vaccination. The design is a significant strength of the study, with randomised controlled

trials widely regarded as a gold standard of study design due to the minimisation of potential sources of bias, and ability for conclusions to be made regarding cause and effect (Hariton & Locascio, 2018). The large sample size also allows for increased power and therefore more confidence in the study findings. There are however drawbacks to randomised controlled trials that should be noted. For instance, they are often criticised for lacking applicability to real world situations or settings, due to strict inclusion and exclusion criteria and highly controlled settings. In the present trial, comparisons to age group norms showed that despite the strict inclusion and exclusion criteria, participants were similar regarding trait affect, perceived stress and quality of life in terms of physical and mental health, indicating that the inclusion criteria may not have impacted real world applicability. However, the exclusion of those who had not received the previous years' vaccination and those over 85 years old means that the population sample is likely to differ from the general older adult population may in these aspects, which may have consequences for applicability. Similarly, it is unclear if the results of this trial would extend to other situations in which influenza vaccinations take place, such as in chemists and pharmacies.

The uptake, recruitment and retention of participants is also a strength of the For-ME study. Indeed, uptake was slightly higher than previous research which demonstrated a response rate of approximately 10% (Ayling et al., 2019; Ayling, Fairclough, et al., 2018), suggesting that the low-intensity single invitation letter approach was successful. Retention was also high, with 94% of consented participants attending the primary clinic session, and 87.5% attending the four-week follow-up session. This is slightly lower than previously reported figures for attending four-week follow-up sessions in

similar trials, which have reported attendance at 98.4% (Long et al., 2012), 96.2% (Ayling et al., 2019) and 93.2% (Ranadive et al., 2014), despite additional measures of reminder telephone calls/texts/emails. Reasons for drop-out were primarily illness related, issues with scheduling, or not attending on the day, presumably due to forgetting or choosing not to attend without proving a reason. Thus, opportunities to improve retention further were limited. Participants were provided with both an appointment letter and reminder phone call or text the day before the appointment, therefore it was felt that this was sufficient in order to minimise forgetting as much as possible, and that any further reminders may be excessive. Scheduling issues were caused by the fact that follow-up visits had to take place exactly four weeks after the initial visit. Given this constraint, the minimal drop-out is noteworthy, and suggests that the measures employed to reduce loss to follow-up were successful. Future trials may want to consider additional measures to minimise drop-out even further, for example by providing a wider range of available sessions to allow a greater possibility of participants being able to attend both sessions at the necessary time-points. However, this is limited to an extent by the availability of space and nurses at each clinic, and needs to be balanced against the possibility of empty time slots that are not filled.

This study provides both novel findings, and support of previous research. This is the first study in the context of the mood in older adults or in the influenza vaccine effectiveness literature to use a choice-based intervention as a means to improve state positive affect. Thus, the finding that the choice-based intervention resulted in significantly higher post-intervention positive mood compared to usual care, whilst showing no significant differences to the standard, no-choice positive intervention is a novel contribution. On the other

hand, the finding that the standard fixed-content intervention also resulted in significantly higher positive mood, with no significant impact on antibody levels, though with trends that point to potential benefits replicates the findings of Ayling et al., (2019). This provides further support to the ability of the standard intervention to significantly improve mood on the day of vaccination, whilst reproducing the unclear findings surrounding the impact on antibodies. Thus, this study constitutes only the second intervention study in the relatively unexplored area of state-affect and immunological response to influenza vaccination, providing valuable insight.

This study also addresses a limitation of the previous feasibility study, which used an active comparator. By using a usual care group as a comparison group, this study has extended previous findings, and allowed the understanding of the additional benefit of the interventions above what is normally expected in standard practice. Further, conducting usual care sessions independently from active intervention sessions addressed a previously encountered limitation of potential contamination between conditions. Whilst the results of the study do indicate that positive mood was significantly higher in both intervention groups compared to usual care, examination of the usual care group showed that positive mood scores also significantly increased in this condition from pre- to post-intervention, albeit to a smaller degree than the active interventions. This could suggest two things. Firstly, that usual care itself results in improved mood in this population. This seems unlikely given that participants did not receive any intervention. The second possibility is that the usual care condition was not necessarily a true reflection of usual care. Indeed, the very act of taking part in research or 'being studied' has been shown to influence outcomes in research (French &

Sutton, 2010; McCambridge, Butor-Bhavsar, Witton, & Elbourne, 2011; McCambridge & Kypri, 2011; McCambridge, Witton, & Elbourne, 2014). Additionally, several processes were slightly altered from standard practice for practicality issues, such as having timed appointments, being in small groups and waiting for a potentially longer period of time. It is therefore possible that this setting provided a social environment where participants could interact, potentially acting as a social interaction intervention, which may have impacted on mood itself.

There are further limitations to the present study which should be considered when interpreting the study results. For instance, antibody responses were only assessed at the four-week time-point. As discussed in Chapter 5 (section 5.4.2), this time-point represents peak antibody response and thus is the critical time-point for determining vaccine response. There were also several pragmatic reasons for not including a second longer-term time-point, including the time and financial implications of analysing an additional 650 blood samples, and increased participant burden. However, the implication of this is that this study cannot speak to the long-term effects of the intervention on antibody response. The long-term effects may be important, as previous research has demonstrated that for at least some strains, vaccine response may begin to decline after four-weeks (Ayling et al., 2019; Kositanont, Assantachai, Wasi, Puthavathana, & Praditsuwan, 2012; Phillips et al., 2006; Pressman et al., 2005). In the present study some participants received their vaccine as early as September, whilst influenza activity is often highest in December and January (Public Health England, 2019d, 2020), suggesting that some participants may not be protected at the point when protection is most needed. Therefore, future work including long-term assessment of vaccination

response may be helpful in understanding long terms response to vaccination, and whether any differences between groups are sustained over this period, thus providing protection throughout the flu season.

Finally, it is worth considering the self-selecting sample of participants, who may not be representative of the general UK older adult population. Indeed, whilst 85.4% of the East Midlands population described themselves as White British in the 2011 Census (Office for National Statistics, 2020), 96.9% of the study population described themselves as White with only 0.9% describing themselves as Black, Asian or Mixed. Whilst evidence suggests that influenza vaccine antibody response does not differ significantly according to ethnicity (Kurupati et al., 2016), it is unclear whether the two interventions are effective in improving mood across different ethnic groups. Thus, not only were study participants not representative of the geographical population, but, as a further consequence, study results may not be applicable to other ethnicities. The issue of poor recruitment of ethnic minorities is well known, with research suggesting that whilst minorities are just as willing to take part in research as non-minority individuals (Wendler et al., 2006), factors such as access to health research and issues surrounding consent and translation/interpretation may be the most important when considering how to address the imbalance (Hussain-Gambles, Atkin, & Leese, 2004; Wendler et al., 2006). Several strategies have been proposed focusing things that researchers can do to improve recruitment of ethnic minority groups, including considering the location of practices to be recruited, the use of special advocacy or community link workers, greater cultural sensitivity in the methods, materials and data collection instruments, and including minority groups in various stages of the research (Hussain-Gambles et al., 2004; National Institute of Health

Research., 2020). In the present study, in order to try to improve the representativeness of the sample, several GP sites with high Black, Asian and minority ethnic (BAME) demographics were recruited. However, rather than this resulting in a better demographic spread and increased representation of BAME individuals, there was poorer recruitment at these sites. This suggests that future trials should implement other suggested strategies to ensure a more representative sample of participants.

7.4 Next steps

Throughout this discussion, a number of next steps have been identified. Of primary importance is a body of work to further the understanding of potential mechanisms and processes underlying the relationship between the intervention, mood and immune response to vaccination. In the context of this thesis, the first step towards such mechanistic studies is to understand the participants' perspectives in terms of how the intervention may or may not have worked in terms of both improvements in mood and antibody response. Therefore, the next chapter describes a qualitative study carried out with a selection of participants of the For-ME study, to gain insight into these perceptions. This study also explored ways in which the intervention and study experience itself can be further optimised for use in a larger, definitive trial. The implications of these results in the wider research context will be discussed in detail in the overall discussion of this thesis.

7.5 Chapter summary

This chapter set out to address the two main aims of the For-ME study, and discuss the findings and implication of these findings. Analysis of the mood-

related data showed that post-intervention positive affect was significantly higher in post intervention groups compared to the usual care group. However, analysis of the antibody data showed that this did not translate to statistically significant differences between groups in terms of antibody levels. The implications of these findings have been discussed, and the next steps in the context of this thesis have been identified. Thus, to further supplement these findings and try to gain an understanding of how the positive mood interventions may have impacted mood, as well as understand and identify ways in which the trial can be further improved from a participant perspective, the next chapter discusses a qualitative study involving a selection of participants from the For-ME study.

8 Chapter 8: Exploring the experiences and perceptions of participants of the For-ME trial: A qualitative study

8.1 Chapter overview

Following on from the randomised controlled trial (RCT) discussed in the previous chapters, this chapter outlines a qualitative study conducted with a sub-sample of participants of the RCT, with two main aims. Firstly, to understand the participants' perceptions of the processes and mechanisms underlying how the interventions may have worked, including how choice may or may not impact mood, and how mood may or may not impact immune response. The second aim was to inform a future definitive trial by investigating whether participants feel that the intervention and/or overall study participation experience can be improved in any way. Thus, this chapter aims to outline the context for this qualitative study, describe the methods used to address these aims, and outline the results in terms of themes and subthemes. Lastly, this chapter will discuss the implications of these findings in terms of their contribution to our understanding of the processes surrounding choice and mood, and any potential consequences for future intervention and/or study design.

8.2 Introduction

The previous chapters describe the development, methodology and outcomes of a RCT, aiming to investigate the effects of two brief mood interventions (compared to usual care) on positive mood, and to assess whether this impacts on influenza vaccination response. In doing so, this study may also be able to inform the design and development of a future large scale trial, that will be powered to detect changes in antibody levels and/or clinical outcomes. The scale of such a definitive trial will have both financial and practical

implications. Therefore, it is imperative that the mood intervention is optimised, in order to maximise potential benefits in terms of mood improvement and antibody response.

As discussed in Chapter 4, there are several explanations as to why the provision of choice may be beneficial, including the enhancement of autonomy and perceived control, which in turn have been linked to positive mood (Grob, 2000; Reis et al., 2000; Sheldon et al., 1996). Additionally, choice may increase personal relevance, which may impact attitude towards the intervention (Lindhiem et al., 2014). However, the link between the provision of choice and positive mood is not well investigated or understood. Therefore, a qualitative study was designed to address several key aims:

i. To explore participants' perceptions and understanding of how and why the intervention did or did not work in terms of the underlying processes and mechanisms regarding:
    a. The relationship between the intervention, mood and vaccine response.
    b. The impact of the provision (or not) of choice on the participants' mood.
ii. To further optimise both the intervention and overall study experience by exploring the participants' experience of the trial and whether any aspect should be changed or improved upon.

8.3 Methods

8.3.1 *Design*

This was a qualitative study using semi-structured interviews.

8.3.2 *Participants*

Participants were recruited from the larger pool of participants who had taken part in the randomised controlled trial. Eligibility criteria for the trial can be found in Chapter 5. Additionally, to be part of the qualitative study, participants had to have been randomised to one of the two intervention arms. Those who had been randomised to the usual care arm were excluded as they had not experienced the brief mood intervention.

8.3.3 *Setting*

Interviews took place over the telephone. This method was chosen to ensure that recruitment was maximised, as it enabled participants to take part at home in their own time and ensured that participation was not limited to those that lived locally or were able to travel.

8.3.4 *Procedure*

Participants were selected using a random number generator that corresponded to their participant ID, and were then purposively selected from the pool of randomly selected participants to ensure that no participants from the usual care arm were invited, and to ensure an equal number of participants from both active intervention arms. Details regarding the number of participants who were approached and who took part in the interviews can be found in Section 8.4.1. These participants were invited to take part in the qualitative study at the end of their second RCT follow-up visit. They were given an information sheet, consent form and pre-paid return envelope, and were given the opportunity to ask any initial questions. They were then told

that a researcher would be in touch by telephone in a few days to provide another opportunity to ask any questions they may have about the study and, if they wanted to take part, arrange a suitable date and time. At this point participants were asked to sign and date their consent form, and return it using the return envelope. This gave the patients time to thoroughly read through the information sheet and consider their decision to take part.

At the start of the interview, all patients were informed of their right to withdraw and given information regarding confidentiality and anonymity. They were given a further opportunity to ask any questions. The interviews followed a semi-structured interview schedule (Box 8.1), in which participants were asked a series of open-ended questions and prompts. A semi-structured approach was adopted to allow for some flexibility for the interview to be guided by the participant, whilst ensuring that all participants were asked the same key questions. The interviews lasted between 20 and 42 minutes (average 29 minutes). A telephone recording connector was used, and all interviews were audio recorded. Upon completion, participants were reimbursed £10 for inconvenience.

8.3.5 *Interview schedule*

The semi-structured interview schedule was formulated through an iterative process involving both discussion with other researchers, and based on Public and Patient Involvement (PPI) group feedback (see section 8.3.8 for further details). A first draft of the interview schedule was developed, and discussed with two other researchers connected to the study. Based on these discussions the schedule was redrafted, and several questions were revised

with the aim of making the question clearer and more refined, as well as the addition of some questions that were felt to be missing. The revised schedule was then discussed again with a second researcher, before a final draft was completed. This was then piloted with the PPI group, following which the draft was finalised (see Box 8.1).

The finalised interview schedule contained a series of open-ended questions and prompts and was split into several sections. Firstly, questions regarding the potential processes and mechanisms behind the potential link between choice and mood were explored. This included questions regarding how the intervention made the participants feel, and why they thought that was, questions about the video clip selection, and whether participants felt that the intervention impacted on their experience of their influenza vaccination. There were also specific questions for those in the choice group and no-choice group regarding what they thought about the ability, or not, to choose their own content.

The second set of questions pertained to the optimisation of the intervention and trial experience. In order to understand participants' experiences of the study, and to investigate whether the experience could be improved further, participants were first broadly, and then specifically, asked about their experiences of the processes involved in the trial, and whether there was anything that could be done differently or improved upon.

Finally, participants were asked whether they would consider taking part in a similar trial again, and whether they would use similar mood enhancement

strategies in future without being part of a trial. This was to assess participants' attitudes towards the intervention in terms of the extent to which they enjoyed the study experience, and the perceived benefit of mood enhancement on vaccine response.

8.3.6 *Ethical issues*

Ethical approval and research governance approval was obtained prior to study commencement at the same time as approval of the randomised controlled trial (REC: 19/EM/0081). The procedures outlined above ensured that all patients were able to fully provide informed written consent. Participants were also made aware of their right to withdraw and assured of their confidentiality. All interviews were recorded using a portable recording device. The data file was then uploaded to a secure computer following each interview and then deleted from the recorder. The interviews were transcribed verbatim by an independent transcriber. Any personal details in the transcripts were removed. These were also kept on a secure computer and were password protected. Both the audio file and transcriptions were kept on the computer using each participants' study identification number, rather than name or any other personal identifying information. Additionally, this was kept separately from personal information such as contact details and demographic data, which were kept in separate secure spreadsheets. Study ID numbers rather than names were also used for the analysis and for reporting the findings.

Process/mechanism:

Introduction: Firstly, thank you for taking part in the study. I'm just going to remind you about the study. We asked you to come in for your flu jab, answer some questionnaires about how you were feeling and watch some video clips. Remind them of the clips/choices.

1.. How did the video clips make you feel? Did they affect your mood? If so, in what way?

1.1. Prompt: relaxed, distracted, happy etc.

2. What do you think it was about the video clips that made you feel that way?

3. For those in the choice arm only: (If not already mentioned) What did you think about being able to choose which clips to watch? Was that a good thing or bad thing?

3.1. Prompt: In which ways good (or bad)?

3.2. Prompt: in what ways bad?

3.3. Prompt: if not mentioned relevance/control etc.: Some people like choosing because it means that they can choose what they like watching most, and some people like it because it makes them feel in control of what they watch – would you say these were not relevant issues for you?

3.4. Prompt: on the other hand, some people don't like choosing because they find the choice stressful or a bit annoying – what do you think about that?

4. What did you think about the selection of videos?

4.1. Prompts: were you happy with the choice of videos or would you have liked more variety? If yes to more variety, what kinds of content would you have liked (e.g., different music, different comedy etc)

For those in the no-choice arm only:

4.2. Prompts: Some people in the study were able to choose what videos they watched, whereas you were given one preselected collection of clips to watch. What do you think of that? Would you have preferred to have been able to choose what to watch?

4.3. Prompt: If you had been able to choose how AND why would that have been better?

4.4. Prompt: Are there any ways in which it might have been not as helpful/effective or actually worse to have choice?

5. Can you remember anything else about your visit that affected how you felt in a good way or bad way:

5.1. Prompt: Let's start with before you arrived at the clinic (e.g., can you remember/tell me what happened that morning, your journey in)

5.2. Prompt: Now let's talk about when you first arrived (e.g., the waiting area, the receptionist, meeting the researchers, the room etc.)

5.3. Prompt: Now how about doing the questionnaires and watching the videos on the tablets (e.g. using the tablet, the volume, the headphones)

5.4. Prompt: Finally, was there anything that affected how you felt after the videos and questionnaires (e.g. getting the flu jab, any waiting time)

6. Do you think watching the videos influenced your experience of having the flu jab and if so how?

Box 8.1: Interview schedule

Optimisation:

7. The aim of this research was to improve your mood just before you have a flu jab because some evidence suggests this is associated with it working better. With that in mind we want to know if there is anything else we can do; or anything we can do differently that might have improved your mood further?

8. Let's go through the experience in the same order as before. Do you think there's anything we could have done differently in terms of before you watched the videos?

   Use what they've said in previous section e.g. if said they didn't like the reception wait, ask what they would have liked/what would make it better

   8.1. Prompts: the waiting room, reception, the researchers, the room

9. How about during the video watching part?

   Use what they've said in previous section

   9.1. Prompt: anything relating to the ipad devices themselves being used to watch the video clips, was the touchscreen okay, was it easy enough to navigate, were the instructions clear?

   9.2. Prompt: How about the room you were in, number of people there with you, the headphones

   9.3. Prompts: The video clips themselves – anything you would have liked to have seen that wasn't there, anything you really didn't like, more choice, less choice, too much/too little variety

10. Now how about after watching the video?

    Use what they've said in previous section

    10.1. Prompt: Waiting for the flu vaccine

    10.2. Prompt: The actual flu vaccine itself

11. Is there anything else you think we could have done differently that would have improved the overall experience?

Future work:

12. Would you be happy to watch videos again in your GP surgery before your flu jab? If yes, why? If not, why not?

13. Is there anything that you've got out of taking part in this study?

    13.1. Prompt: would you do anything differently for your next flu jab because of this study?

    13.2. Prompt: would you consider trying to get yourself into a positive mood before future flu jabs?

14. Are there any other ways you would try to get yourself in a positive mood, other than watching video clips?

15. Is there anything else you would like to add?

    15.1. Prompt: anything else about today or about the study

Box 8.1: Interview Schedule continued

8.3.7 *Data analysis*

To address the various aims of the study, different approaches to analysis were adopted. To investigate potential underlying processes and mechanisms, an inductive thematic analysis was used (Braun & Clarke, 2006). This was considered an appropriate approach due to the nature of the experience of interest, which was a one-off event that may not have carried a great deal of meaning or significance to the participants. The thematic approach allows for the identification and development of themes to describe, organise and understand the experiences of participants, without the requirement for very rich data. Thus, thematic analysis was carried out in a bottom-up fashion, remaining closely linked to the original data. Analysis took place using NVIVO (released March 2020), and involved several stages, following the guidelines described by Braun and Clarke (2006).

Firstly, all interviews were listened to and each interview transcript was read several times, allowing full immersion in the data. Initial thoughts and ideas were recorded. After the reading and immersion phase had been completed, initial codes were generated and collated. Codes were created from all transcripts manually, using both descriptive and interpretive codes. Codes were assigned to as much of the data as possible, and multiple codes were sometimes assigned to the same segment. The next stage of analysis involved refining the generated codes. All codes were indexed into groups of potential themes and subthemes which accurately depicted the data, by identifying patterns in the codes. This process was not linear, and often required groupings to be reworked. Some codes did not naturally fit in to a thematic grouping, and so a ‘Miscellaneous’ grouping was created. Once all codes had been grouped, efforts were made to assign those codes within the

‘Miscellaneous’ grouping to an existing group, or to a new thematic grouping. Finally, themes and subthemes were reviewed and refined. Review of the themes and subthemes occurred on two levels: firstly, at the level of the coded data, to ensure that the collated codes formed a coherent pattern, and secondly at the level of the dataset, to ensure the themes reflected the data as a whole. A thematic map was drafted, including all generated themes and subthemes. This was an iterative process that occurred alongside periodic discussion with another researcher, resulting in further refinement of the themes and subthemes, as well as further drafts of the thematic map (Appendix I).

To address the second aim of the study, which was to identify areas for optimisation for a future definitive trial, a thematic-content hybrid approach was used. Whilst the thematic approach was deemed appropriate to understand the experiences of the participants in terms of what worked and did not work for them during the course of the study, a content-analysis approach supplemented these data by quantifying and outlining definitive areas to target for optimisation, and allowed for a set of recommendations to be made for a future trial. Content analysis has previously been critiqued as it can lead to the oversimplification of complex communication (Kracauer, 1952). Thus, a hybrid thematic-content approach allowed the research aims to be addressed, resulting in a quantifiable output, whilst also accounting for the richness and complexity of the data. Content analysis was carried out according to the conventional approach (Hsieh & Shannon, 2005), with an initial coding scheme developed directly from the data, focusing on aspects that could be improved, as well as those requiring no change. After an initial scheme was developed, each transcript was analysed. The entire transcript

was assessed, but with particular focus to questions 7-11. Code units were conceptual, so that codes did not have to have the same wording, as long as the meaning was the same. As with the thematic analysis, codes were a mix of descriptive and interpretative, with slightly greater emphasis on descriptive codes. The codes were then categorised into those relating to the intervention specifically, and those relating to the general study experience. These codes were then tabulated, with a count of how many participants the codes had been generated from. They were summarised narratively, with any noteworthy aspects, or those specifically identified by participants as being particularly disliked or liked, highlighted.

8.3.8 *Patient and public involvement (PPI)*

The benefits and importance of PPI group involvement are discussed in Chapter 5. PPI group feedback informed this qualitative study in two ways. Firstly, the group was consulted on whether qualitative interviews were a reasonable and acceptable approach to address the research aims. In response to this, the group indicated that they thought it was an acceptable idea, and something that they would have been happy to participate in. The group did emphasise that the interviews should take place quite soon following the intervention, as they personally (and therefore potentially participants more generally) may otherwise have issues regarding memory and recall. Secondly, the group provided feedback regarding the interview schedule itself, based on their experiences of a version of the intervention that the group had just tested. The primary aim was to ensure that the questions were appropriate and easy to understand, and to assess whether there was anything that needed adding. This was carried out in two ways. Half of the group went through the schedule together to provide general feedback

regarding the clarity and appropriateness of the questions. The other half of the group provided contact details to pilot the schedule individually at a later time over the phone. They provided feedback on the comprehensiveness and experience of answering the draft questions. Across both methods of feedback the questions were deemed appropriate, with no additions needed. Therefore, no changes were made to the schedule.

8.4 Results

In total, 17 participants took part in the qualitative interviews. All 17 were purposively selected from a pool of 39 randomly selected participant IDs (35 excluding those who took part in the usual care arm of the RCT). Purposive selection of participants was carried out to ensure that there was a roughly even number of participants from both the choice intervention group and standard intervention group. Of the 35 participants, four could not be invited as they did not attend the follow-up appointment, one declined to take part for unknown reasons, and one did not attend the scheduled interview due to illness. Thus, a total of 31 participants were invited, and 17 interviews were conducted, at which point it was agreed that data saturation had been reached and so no further interviews were arranged. Figure 8.1 shows the flow of participants through the study.

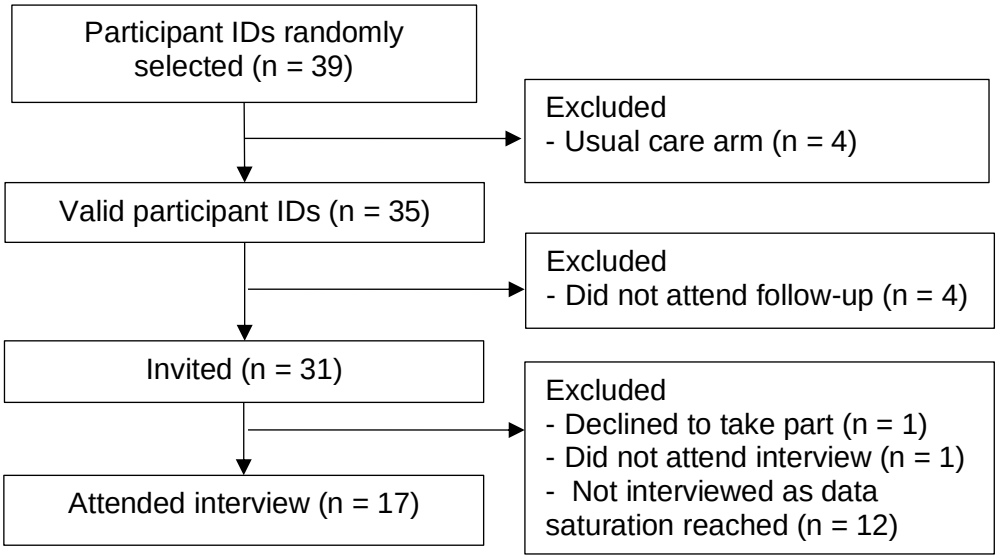


Figure 8.1: Flow of participants

8.4.1 ***Demographics***

Table *8.1* shows the demographic and study-related characteristics of the interviewed participants. The age of the participants ranged from 65 to 82, and majority were female. Participants represented ten of the 13 GP practices involved in the trial, and were proportional to the number of participants from each practice participating in the trial. There was an approximately even split between those who had received the choice-based intervention (47.1%) and those who had received the no-choice intervention (52.9%).

Table 8.1: Summary participant demographics

Participant ID	Age	Gender	Intervention arm	GP practice
023	82	Male	No-choice	4
070	67	Female	No-choice	8
073	71	Female	No-choice	4
074	73	Female	Choice	4
222	70	Female	Choice	11
252	65	Female	No-choice	11
276	71	Male	No-choice	9
325	76	Female	Choice	7
394	68	Female	Choice	7
420	69	Female	Choice	5
439	70	Female	No-choice	4
448	70	Female	Choice	12
494	66	Male	No-choice	5
558	65	Male	Choice	9
589	70	Female	No-choice	2
601	69	Male	Choice	6
706	68	Female	No-choice	13

8.4.2 ***Themes***

8.4.2.1 Processes and mechanisms

Four themes regarding the potential processes and mechanisms underlying the relationships between both choice and mood, and mood and vaccine response were developed. These are presented, alongside their sub-themes in Table 8.2. ‘Type of content’ describes how and why the perceived impact of

the intervention video clips on participants' mood varied by different features of the specific clips. 'Barriers and facilitators to mood change' explores both why participants may or may not have experienced mood change in response to the intervention, as well as future intentions regarding mood change. 'The study experience' describes how the research experience itself may have impacted mood and/or vaccine response. Finally, 'the value of choice' explores participants' views regarding the provision of choice, and how this differed among the intervention arms. Each of these will now be discussed in turn, using quotes to illustrate. The bracketed information following each quote states the participant number, gender ('F' indicates female and 'M' indicates male) and intervention group ('C' indicates choice group and 'NC' indicates the no-choice group).

Table 8.2: Themes and subthemes regarding the processes and mechanisms of the intervention

Theme	**Subtheme**
Type of content	Old versus new
	Familiar versus novel
	High versus low arousal
Barriers and facilitators to mood change	Level of evidence
	Prior beliefs and experiences
	The impact of state or trait mood
The study experience	Comparisons between the study and the normal flu clinic
	The effect of social interaction
	The intervention versus the study
The value of choice	Positive and negative aspects of choice
	Variation in the value of choice

Type of content

There was variation between participants in whether they felt the intervention impacted their mood or not, and whether or not they enjoyed the intervention. Thus, this theme explores the aspects of the intervention content that may have impacted both of these factors to explore why and how the participants perceived the intervention to have (or not) worked.

Old versus new

Participants identified that many of the video clips included in the intervention were old. Some participants viewed this as a positive, suggesting both that older content was of a higher quality that was still funny today, as well as citing negative experiences with more modern content. Participants also felt that the older content may be more appropriate given the age of those receiving the influenza vaccine.

> *My immediate reaction is that present day stand-up comedy, and I'm just thinking because you're looking at the generation that you're looking at and that sort of thing probably does not appeal to people of my generation. [Participant 394, F, C]*

On the other hand, some participants, such as the participant below, appreciated the inclusion of some more modern clips, citing that they liked the variety, whilst a minority of participants felt that there should have been a greater proportion of modern, contemporary content.

> *I think generally the mixture was quite good and quite right and for a 15-minute slot, it touched the spot as they say. [Participant 494, M, NC]*

Familiar versus novel

This subtheme overlaps, to some extent, with the previous subtheme "old versus new" in that participants tended to be more familiar with older clips, describing them as '*age old*' and '*classic*'. However, some participants were also familiar with more modern clips as they were from television shows or sitcoms that they would normally watch on television anyway. One of the benefits of this familiarity was that participants knew that they would enjoy the content, and for some, the anticipation of knowing the punchline made the experience even better.

> *Well, you start chuckling before you've even seen what's happened, because you know what's going to happen - it makes you chuckle. [Participant 589, F, NC]*

Another benefit of familiarity with the content was the experience of reminiscing and nostalgia, which some participants cited as the main reason for enjoying the clips. For instance, several participants discussed how certain clips brought back happy memories, as well as emotional associations with family members.

> *It also goes back to as I say happier times and even as far back as when my mum and dad were alive. It's sort of like a continuity and a feeling of when life was more predictable and more understandable than it is these days. [Participant 074, F, NC]*

On the other hand, some participants felt that familiarity reduced the impact that the clips had. For these participants, knowing what was coming was less

enjoyable. Instead, novelty was more important and had a greater impact on mood.

> *It's the element of surprise when something happens that can humour you. But if you've seen it more than once and you know what's coming then it doesn't surprise you. [Participant 276, M, NC]*

High versus low arousal

Many participants reported reasons related to high arousal, or activation, as to why the intervention improved their mood, such as finding the clips funny, or being made to laugh. Alternatively, others cited that the main reason for their mood improvement was low arousal effects of the clips. For instance, several participants described the intervention as relaxing, and that watching the clips was a good distraction from things going on in their lives or from anxieties about the vaccine or blood test. For these participants, it appeared that enhancing positive mood may not be as important as reducing negative mood. This suggests that the same clips might have positive effects for different reasons. This also extended beyond the intervention experience to general responses to life events, with participants describing how they might negate negative emotions through relaxation or distraction, rather than try to enhance positive emotions.

> *Everybody's got something on their mind and it does take it away to a certain extent yeah. [Participant 222, F, C]*

> *And if something negative has happened in that respect you can't probably do anything about it, apart from trying to clear your mind about it. So perhaps something like going to, maybe doing Tai Chi or*

something like that would, in that sort of instance help clear your mind in a way. [Participant 439, F, NC]

Several participants discussed ideas for other content that did not involve high arousal humour. Specific examples included 'feel good' content such as children playing, animals, weddings, as well as more relaxing content such as nature or environmental based content. For these participants, humour was less important, and they felt it did not necessarily improve mood. Thus, this demonstrates the presence of individual differences, not only in terms of the impact of the same clips on different participants, but also in terms of preferences for high or low arousal based content.

Barriers and facilitators to mood change

Theme two explored the potential barriers and facilitators to participants' mood change. There was variation in terms of whether participants felt the intervention resulted in a change to their mood, and whether they would attempt to change their mood of their own accord in the future, prior to receiving a influenza vaccine.

Effect of existing mood

For some participants, the ability of the intervention to improve their mood depended on their mood on the day of the study. For instance, participants already in either a very good, or very bad mood on the day of the study were less likely to report intervention related changes to their mood.

I was quite happy when I came in so I don't think they would have made me feel any different. Probably couldn't have improved on how I felt. [Participant 252, F, NC]

This finding has been also been linked to the quantitative analysis of the trial (Box 8.2).

As well as state mood, an individual's perception of their trait mood may influence the perceived benefit of a mood enhancing intervention, and whether they would adopt positive mood-enhancing strategies in the future. Those who described themselves as generally positive people saw little need for mood enhancement, and so were less likely to find benefit in implementing such strategies in the future.

The point is I am usually pretty positive anyway, so I don't know why I would try to do that [improve my mood] and I don't know how you can. [Participant 706, F, NC]

Some participants reported that others who were in a poorer state mood (i.e. worried or anxious about the influenza vaccine) or poorer trait mood (i.e. generally not that happy), may have greater benefit compared to themselves.

Somebody who was probably not feeling quite as happy as me, then I would have expected the short clips would have probably lifted their spirits. [Participant 558, M, C]

Given the above finding regarding the impact of pre-existing state on the impact of the interventions on state affect, relevant quantitative analysis was also carried out to assess whether this qualitative finding was consistent with the quantitative data.

Analyses based on tertiary splits showed that there were significant differences between those scoring in the lowest and highest thirds on pre-intervention state affect. Those scoring in the highest third in terms of pre-intervention state positive affect (PA) had significantly higher post-intervention state PA but significantly lower change from pre- to post-intervention scores compared to those scoring in the lowest third.

Table 8.3: Differences in post-intervention state PA and change from pre- to post-intervention state PA between those scoring in the lowest and highest thirds in pre-intervention state PA

	Lowest third Mean (SD)	**Highest third Mean (SD)**	**P value**
Post-intervention	71.19 (16.92)	96.73 (5.44)	< .001
Change from pre to post	14.10 (15.74)	0.16 (5.19)	< .001

Note: Mann-Whitney U test was performed due to violations in the assumption of homogeneity of variance

Box 8.2: Link to quantitative analysis

Prior beliefs and experiences

Prior beliefs and experiences impacted the perceived benefit of the intervention and of attempting to improve owns one mood. For instance, some participants believed that they could not influence their mood, and saw it as stable and unchanging. Some participants also believed that their mood was only impacted by external factors that cannot be influenced and is therefore down to luck or chance. These participants were less likely to report that they might try to improve their own mood in the future.

> *The things that might change my mood are things that are going on in your life or in other people's lives that you have no control over.*
>
> *[Participant 439, F, NC]*

I don't get really excited about anything, I don't get really down about anything… generally on a day to day basis I'm pretty steady mood. [Participant 252, F, NC]

Expectations regarding the intervention and study experience may also impact perceptions of the intervention. For instance, participants reporting lack of expectations concerning the intervention and study and an open-minded approach were more likely to report that the intervention did alter their mood state.

We weren't apprehensive at all, we were open minded… and both my wife and myself were pleased with what we saw. [Participant 023, M, NC]

Previous experiences with influenza and the influenza vaccine also appears to influence a participant's perceived benefit of mood enhancement and thus their intentions for mood improvement in the future. For instance, believing that the influenza vaccine is already effective enough meant that some participants felt they did not need to improve on its effectiveness by enhancing their mood.

So, in some ways possibly you would say that statistically it can't really be more effective for me because most of the time it has been effective for me anyway. [Participant 394, F, C]

Finally, beliefs regarding the relationship between the mood and the influenza vaccine may also influence future intentions regarding mood change.

Participants who believed that mood can impact physical health were more likely to say they might try to improve their mood in the future, whereas those who saw mood and vaccine response as separate were less convinced there was a need to. Interestingly for some participants who believed that mood may impact vaccine or health outcomes, the belief that state mood could not be changed outweighed this.

> *It's a physical thing isn't it? It's a physical thing you're doing to somebody. So the fact they're in a happy mood or an unhappy mood I wouldn't have thought it made any difference really to the physical, whatever physically you're trying to do. [Participant 276, M, NC]*

Requirement of evidence or 'proof'

There was variation between participants in the level of evidence or 'proof' that they would need that enhancing positive mood may be beneficial for influenza vaccine effectiveness before they would consider trying to enhance their own mood before future vaccinations. For some, the level of evidence needed was low, as it was seen as something easy to do with few drawbacks.

> *Well, it can't hurt, it can't hurt can it, to do that. [Participant 420, F, C]*

On the other hand, some participants required a much higher level of evidence before they would consider mood enhancing strategies in the future.

> *I wouldn't just start jumping through hoops just on somebody's whim. I'd have to hear a little bit of convincing evidence. To actually do something, I'm quite happy to go along with you anyway at the moment, but you're asking me if I would be happy to do something*

myself to help matters. Well I would but only if I was satisfied that it was definitely an improvement, beneficial. [Participant 276, M, NC]

The study experience

There was a distinction between the intervention itself and the study experience as a whole. Therefore, this theme explores how the experience of taking part in the study may have impacted mood irrespective of the intervention, and how the study experience may have influenced the experience of the intervention.

The effect of social interaction

Intervention sessions took place in small groups of up to seven people. For several participants this was a positive aspect that enhanced the study experience as it made it a more social event. This was identified as particularly important by one participant who noted the damaging effect of social isolation and loneliness in the older adult age group. Having someone else that they knew in the group also put some participants at ease. An additional aspect of the group setting was that it allowed participants to observe how others were responding to the intervention, and in some cases seeing others laugh increased their own mood and led to conversation between participants.

But by the time we'd all finished and heard each other laughing and started a conversation about what did you watch and oh I wished I'd watched that or oh that sounded good and all the rest of it… we were just laughing at him laughing. [Participant 394, F, C]

Conversely, other participants did not experience interaction within their groups. This suggests that environment or group dynamics may have impacted participants experiences of the study.

> *The participants didn't talk to one another at all. It wasn't that sort of environment. [Participant 439, F, NC]*

Comparisons to standard flu clinic

Several participants made comparisons between the study and the standard flu clinic. For some, the intervention was a better experience, as they felt less rushed and more significant, with some participants comparing the normal flu clinic to a production line or cattle shed.

> *It was quite nice to be welcomed and to watch something silly instead of being rushed in and jabbed and off out. [Participant 589, F, NC]*

Another benefit over the standard flu clinic was the fact that participants were given a pre-arranged appointment, which gave reassurance that they would receive the vaccine, whereas standard drop-in flu clinics can lead to feelings of pressure and unpredictability. Finally, some participants noted anxiety regarding having to mix with a lot of other older adults at standard flu clinics, citing concerns regarding passing on germs.

For other participants, the speed of the standard flu clinic was an advantage and preferred over the longer appointment with the study visit.

> *If it was a choice of going for a flu jab, in and out in five minutes thank you very much or going in for half an hour and watching 15 or 20 minute videos to have the flu jab I think I'd go for the former rather than the latter. Once you're there you want to get on with it and get out. [Participant 494, M, NC]*

Others reported no preference between the two experiences.

The study versus the intervention

For some participants, the experience of the overall study and the experience of the intervention itself were distinct. One participant described that whilst they felt that the intervention itself did not lead to an improvement in mood, taking part in study activities such as filling in forms and completing questionnaires was enjoyable. Thus, for some participants, the act of taking part in the research may have had a bigger impact on mood then the intervention itself.

> *The whole process of coming in and doing the research. I was interested in that. So I suppose that would have, the whole experience of that, leaving aside the bit of the [video] clips, the filling in the forms and taking part and feeling that I was doing something useful. [Participant 439, F, NC]*

Alternatively, for some taking part in the overall study may compliment the intervention and contribute to mood enhancement. For instance, some participants reported that taking part in the study made them feel useful, which may contribute to an improved mood and thus add to any effects of the intervention.

You feel as though you've been useful if you've helped in some way. [Participant 074, F, C]

For other participants, their approach to the study influenced their experience of the intervention. For instance, some participants reported that they were more receptive to the intervention content because of the research context, which they may not have adopted in other circumstances.

The value of choice

Whilst some of the participants were provided with a choice of video clips to watch, others were given a standardised no-choice version of the intervention. This theme explores how participants in both groups view choice, and the differences observed between the groups in these views.

Positive and negative aspects of choice

Both positive and negative aspects of choice were identified by participants. Participants liked that the choice intervention gave them control over what they watched and said that choice was preferable to being told what to watch, or watching something based on someone else's opinion.

I would rather have a choice myself than someone just giving you something that you have no, I would rather have control is what I'm saying, some choice anyway. [Participant 074, F, C]

Another positive aspect of choice was that it meant that participants could select clips that they knew they would enjoy and thus choice enables personal selection. Participants noted how humour is subjective and there are

individual differences in what people find funny or enjoy watching. Therefore, choice increased the likelihood of participants finding content they would enjoy and increased enjoyment of the intervention.

> *I would have picked things that I know that I'd perhaps seen in the past that made me laugh and made me chuckle more than others, so, again, it's personal taste, isn't it? [Participant 706, F, NC]*

> *Because no two people are the same, are they, so it's a good idea to be able to choose. [Participant 601, M, C]*

On the other hand some participants felt that too much choice may be overwhelming and time consuming, whereas too little choice may mean that none of the options are suitable. Additionally, choice may be effortful when all presented options are suitable. Thus, choice is a balance where both too much and too little choice may have negative consequences.

> *Choice is a positive thing, but if you've got loads upon loads of things to choose from… you don't know what you want to watch out of that lot. It depends on how many things you've got to choose from I suppose, if you've got to go down the list and say oh I'm fed up with this, I'll just watch anything. [Participant 070, F, NC]*

> *It's helpful, but it's got to be a fairly wide choice I think, especially with something like music for instance. [Participant 276, M, NC]*

Variation in the value of choice

There were differences in participants' perceptions of choice depending on the group they were allocated to and whether or not they enjoyed the intervention. For instance, participants in the no-choice condition who enjoyed the intervention were indifferent to the idea of being provided with choice, with some saying that it would not have made an impact.

> *No, I was happy with what I got. I don't know, I like the Two Ronnies so I don't think I probably would have chosen anything else. [Participant 252, F, NC]*

Conversely, those in the no-choice group who did not enjoy the intervention reported that the provision of choice would have been beneficial.

> *I would have known what was coming, and I would have felt more in control of what was happening possibly. That I wasn't being dictated to. [Participant 439, F, NC]*

Those in the choice group were more likely to report that they valued choice and thought that not being given choice may have had negative consequences.

> *If you had said you're going to watch some stand-up comedy and there'd been no choice… I think that would have sort of initially brought in a negative response to me because I think I would have thought I don't want to do that. [Participant 394, F, C]*

8.4.2.2 Optimisation of the study: thematic analysis

Three themes regarding potential ways in which the study could be further optimised were identified, as well as highlighting some that already worked well (see Table 8.4). 'Constraints of the context' describes how the study is somewhat restricted by the contextual issues and expectations. 'The study organisation' explores aspects of the study that worked well, as well as some factors where there was variation in participants' views. Finally, 'the important of atmosphere' describes factors relating to the atmosphere that contribute to a good study experience, as well as ways to further improve this.

Table 8.4: Themes and subthemes regarding the optimisation of the study

Theme	**Subtheme**
Constraints of the context	Clinical environment
	Variation in facilities
The study organisation	Being in a group
	Timing
	Pleasant experience
The importance of atmosphere	Friendliness
	Familiarity
	Refreshments

Constraints of the context

This study was a multisite trial that involved several clinical aspects, including taking blood samples and administering the influenza vaccine. This theme explores how this context may have affected participants' experiences of the study.

Clinical environment

Participants discussed ways in which the environment could be more comfortable, however they acknowledged that GP practices are limited in what they can do in that respect. Additionally, participants pointed out that there are certain expectations regarding the environment when having clinical procedures, and thus the clinical setting was appropriate.

> *Because if you're doing that sort of thing [clinical procedures] you would expect it to be in that sort of place. [Participant 439, F, NC]*

Variation in facilities

There was variation between practices in terms of the facilities that were available to the participants and research team. For instance, both room sizes and parking facilities were identified by some participants as causing issues, whereas others reported no problems.

The study organisation

There was some variation in participants' views on some aspects of the study organisation, in terms of the group setting and the duration of both the intervention and study as a whole. Overall, there was a general perception of the study experience being a pleasant and straightforward one.

Being in a group

Many participants found group sizes, which ranged from one to seven (median six participants), to be about right, stating that a larger group may have had implications in terms of timing or space. Those in smaller groups said the experience was quite relaxed.

I thought it was fine, yeah. I don't think, probably if there'd been more it wouldn't have worked so well but I thought it was fine. [Participant 252, F, NC]

Some participants liked the group element and being with others whilst completing the study, whereas others reported that they would have preferred a one-to-one format.

I prefer one-to-one… it's a bit stressful all the people in the room. [Participant 601, M, C]

When I realised we were all going in together, you know, I was quite happy really. [Participant 420, F, C]

Timing

There was some variation in participants' views on the duration of the study. Some participants reported that being retired meant that they had more free time, and therefore the time that the study took up was not disruptive to their day.

I mean efficient is good for some people, but we're all over 65 and retired basically, so we've all got plenty of time. [Participant 706, F NC]

Others suggested a longer duration would be acceptable and could have additional benefits such as more time for socialising or watching more clips. Alternatively, some participants preferred the speed and efficiency of the standard flu clinics and would prefer to '*get on with it*'.

Pleasant experience

Many participants reported that the study experience was a pleasant one, that was straightforward, and for some may have reduced anxieties regarding the flu vaccine itself. For many the experience was relaxed and participants '*went away happy*'.

> *I came away from it thinking oh that was quite nice… Yeah just a pleasant experience. [Participant 448, F, C]*

The effect of the atmosphere

Many participants mentioned aspects relating to the atmosphere of the environment, when discussing both what went well in the study and what could be improved.

Importance of a friendly environment

The friendliness of the practice staff and researchers was often commented on by participants when discussing experiences of the study. A minority of participants reported feeling their GP practice is not very friendly more widely, and this had a knock-on effect on how they felt at the beginning of the study, resulting in a more negative frame of mind. This may emphasise the importance of creating a friendly environment to maximise the potential for mood enhancement.

> *The staff there call you by your first name and they're all friendly and chat to you. If they're not too rushed off their feet they'll always have a chat with you, so I think that helps as well. [Participant 070, F, NC]*

I always find the experience [going to my GP practice], and I'll qualify this in a moment, I don't think you feel too friendly or welcome… So that, I think that has a negative impact on your experiences at the practice. [Participant 494, M, NC]

Familiarity with the environment

In addition to a friendly environment, several participants noted that being familiar with both the surgery itself, and the procedures involved in the study such as having a blood sample taken, contributed to feeling at ease and reducing anxieties.

I do know my way about the surgery. So, I didn't have any anxiety about which room or anything like that. I think if somebody had been unfamiliar with the building, only just going downstairs they might have wondered. But for me personally I found nothing to get anxious about. [Participant 074, F, C]

Improving the atmosphere with refreshments

Participants felt that offering refreshments may have several benefits regarding the study experience. For instance, some noted that a cup of tea or coffee may enhance mood in itself. Others suggested that refreshments would help to make the atmosphere more welcoming and relaxed, whereas others felt that it would benefit the experience by shifting the focus from a formal medical setting to a more social situation.

I know you weren't there for a tea party, but you know, those things just help people relax and maybe just give people time just to get into the zone and into the environment. So probably a cup of tea or cup of

coffee option would have probably just relaxed people more. [Participant 494, M, NC]

8.4.2.3 Optimisation: content analysis

This section outlines the specific elements of both the intervention and the overall study experience identified as (1) areas to be improved for future iterations of the study, and (2) those that already work well and should be retained. As outlined in Section 8.3.7, content analysis was used to quantify areas for improvement and those that worked well using codes.

Table 8.5 outlines participants' ideas for optimisation of the intervention and study experience that were identified through content analysis. Overall, 11 participants reported that the intervention had some positive impact on their mood, compared to six who reported no impact. Of those who perceived that the intervention did not work, reasons varied and included pre-existing mood (either already being happy or being worried or sad), and simply not enjoying the intervention content. For instance, two aspects relating the intervention itself were identified for future improvement. Firstly, five of the 17 participants suggested other intervention content ideas. Of these five, three participants suggested specific content ideas e.g. specific comedians or sitcoms, whereas two participants suggested other types of content relating to nature or animals. Secondly, of the five participants assigned to the choice intervention that offered an opinion on the number of choice options, four felt that the number of options was about right, whereas one participant said that they would have liked a greater number of choice options.

Regarding the study experience itself, several aspects were identified as areas to improve or other factors to consider. Almost half of participants (n=7)

mentioned the provision of refreshments as either something they would have enjoyed or would have improved both the atmosphere and participants' comfort. Two participants described the room as too cramped or uncomfortable. Other participants mentioned issues with the practice's current parking facilities as causing stress and waiting room facilities such as magazines as a way to enhance the experience. Three participants identified that more information prior to the study regarding things such as timings and what to expect would have been beneficial. Other ideas for optimisation were identified by single participants, and included reducing the wait time, having more detailed instructions for the intervention, being introduced and seated with other participants, preferring a one-to-one format and unfriendliness of reception staff.

Table 8.5: Ideas for optimisation of the study and intervention

	Number
Relating to the intervention	
- More choice options	1/8
- Other intervention content	5/17
Relating to the study experience	
- **Facilities**	
o Refreshments (tea, coffee, snacks)	7/17
o Bigger room/room too cramped	2/17
o Issues around parking (time limits/payment)	1/17
o Magazines to read during wait	1/17
- **Procedural**	
o More information before the study	3/17
o Reducing the waiting time	1/17
o More detailed instructions	1/17

	Number
○ Being seated with rest of group in the waiting room	1/17
- **Format**	
○ One-to-one rather than group	1/17
- **Other**	
○ Friendliness of reception	1/17

As well as areas to improve, participants identified aspects of both the intervention and study experience that they felt required no change. These are listed in Table 8.6. Within this, some participants commented on particular aspects that they specifically liked. For instance, of the 12 participants that considered the video clips to be appropriate and had no ideas for alternative content, seven specifically said that there was a good selection, and that they particularly liked or enjoyed the video clips. In terms of aspects relating to the study more generally, all 17 participants reported having no issues with the tablet devices, indicating that this digital platform is acceptable in this age group, even to those without previous experience. Further, one participant indicated that the tablet devices were better than using pen and paper for this type of activity. Of the ten participants who specifically identified no problems or issues with the surgery and/or research staff, nine commented specifically on how staff were welcoming, polite or helpful, which, for some, helped put them at ease. Twelve participants found the instructions and questionnaires straightforward and clear, and one participant in particular identified the Dynamic Visual Analogue Mood Scale (D-VAMS) questionnaire as enjoyable to complete. Twelve of the participants had no objections to the group format of the study. Five indicated that group sizes were appropriate but any larger would have been problematic. Additionally, four participants specifically

reporting that being in a group enhanced the experience, due either finding it reassuring or because the social interaction made it more enjoyable.

Table 8.6: Areas identified as requiring no change

	Number
Relating to the intervention	
- Number of options	4/8
- Intervention content	12/17
Relating to the study	
- Tablets/headphones	17/17
- Being in a group	12/17
- Tablet instructions/questionnaires	12/17
- Friendliness of staff	10/17
- Wait time/waiting room environment	10/17
- Room size	8/17
- No ideas how to improve experience	6/17

8.4.3 ***Statement of reflexivity***

Part of this process involved being reflexive and examining my own role and potential biases in the collection and analysis of the data. I therefore considered my position as a young, female PhD student who had been heavily involved in the design, development and daily running of the randomised controlled trial that the participants had taken part in. I recognised I had spent a large amount of time running the trial, as well as the previous work I had done regarding the role of choice, and the development of the choice intervention. Therefore, I was aware during the interviews that I needed to make sure I was not biased or defensive of the intervention during my questioning. I was also careful to make sure that I put aside any preconceived

expectations or hopes in terms of how both groups experienced the intervention, and how experiences may have differed between groups. I was careful to remain open to differing responses and views regarding the trial, and to encourage both positive and negative feedback. I was also aware of my relationship with some of the participants where I had been the researcher at the GP site and so had previously met and interacted with them, and that some were aware that this research was part of my PhD. I was concerned that this may result in participants holding back on negative opinions for fear of hurting feelings. As such I made it clear at the beginning that I was interested both positive and negative experiences. Further, as interviews were conducted over the phone the potential impact of this previous relationship or knowledge was reduced as participants were less likely to remember me. In the end there was a balance of positive and negative feedback from participants in the interviews, suggesting that these measures were successful.

As part of the reflexive process, I kept an interview diary, which I completed at the end of each interview. As well as being an exercise in reflection, this also enabled me to record and explore any methodological issues, and anything of particular note or interest that occurred during the interview, such as potential themes or differences between interviews. I used this to reflect on how I had experienced the interview, including anything I found particularly surprising or that challenged my own beliefs. I found this helpful as it allowed me to identify and consider how my own beliefs and assumptions may impact the research, and also helped me to reflect on how this may impact on subsequent interviews. Further, it allowed me to discuss aspects I found challenging with another researcher involved in the study to explore suitable ways in which I

could handle those challenges if they occurred again in subsequent interviews.

8.5 Discussion

The present study aimed to qualitatively explore the experiences of participants taking part in one of the brief positive mood interventions before receiving their annual influenza vaccine. This section will discuss the findings of this study in relation to the literature, describe the study's strengths and limitations, and discuss implications and next steps for the research. The study findings will be discussed firstly relating to patient perceptions of the potential processes and mechanisms of the intervention, and then in relation to the optimisation of the study and intervention according to the participants' feedback.

8.5.1 *Potential processes and mechanisms of the intervention*

According to the participants' accounts, the impact of the intervention on participants' mood seemed to be influenced by the factors surrounding the specific intervention content; specifically the age of the clips, the degree of familiarity, and the level of arousal, or activation, associated with the clips. Most participants commented on the older video clips, describing them as classic, whilst referring to more modern comedy as too adventurous and less appealing. This is supported by findings that in general, older adults are more likely to watch television programmes set in earlier times, compared to younger adults (Mares & Sun, 2010). A potential explanation for this may be the perception that modern content is more likely to be offensive, with analyses of media consumption trends across different age groups showing

that American older adults are more likely to be offended by profanity on TV, compared to younger adults (Jones, 2004). Indeed, one of the participants did report that they found modern stand-up comedy offensive and so avoided it. Thus, the age of the content may have contributed to the effect of the intervention on mood.

Nostalgia and reminiscing also seemed to contribute to enjoyment of the intervention for many participants, with participants reporting that certain clips reminded them of fond memories and people. It has been suggested that nostalgia may be particularly important to older adults, as it is important for identity development as adults age (Gauntlett & Hill, 2002). Whilst some research has found nostalgia to result in negative effects, other research suggests that nostalgia may act as a psychological resource with several benefits, including heightening positive mood, increasing positive self-regard, reinforcing a sense of social connectedness and providing existential meaning (Routledge et al., 2011; Wildschut, Sedikides, Arndt, & Routledge, 2006; Wildschut, Sedikides, Routledge, Arndt, & Cordaro, 2010). Similarly, familiarity with stimuli has been associated with several positive responses including increased liking (Bornstein, 1989), smiling (Winkielman & Cacioppo, 2001) and satisfaction (Söderlund, 2002). Thus, this evidence supports the notion that both familiar content, and content eliciting feelings of nostalgia may have numerous beneficial outcomes for this age group, including increasing positive mood. This may therefore be a mechanism through which the interventions in the randomised trial enhanced mood.

Finally, there appeared to be individual differences in the reasons given for reporting post-intervention mood improvements, in terms of high or low arousal. For instance, for some participants, the experience of high arousal related states was given as an explanation for enjoying the content (such as finding it funny and making them laugh), whereas for others, low arousal states (such as relaxation or distraction) were cited. There is limited research on the differential effects of high versus low arousal positive affect in the context of immunity, however there is some evidence to suggest that high arousal positive affect may be associated with greater autonomic activation and fewer colds following exposure to rhinovirus or influenza A (Cohen, Alper, Doyle, Treanor, & Turner, 2006; Cohen et al., 2003). Conversely, other studies have found no differences between high and low arousal positive affect on antibody responses to the hepatitis B vaccine or immune response to mood induction (Futterman et al., 1994; Marsland et al., 2006). The present study suggests that both high and low arousal positive affect stimuli may be beneficial to participants in terms of mood outcomes, potentially depending on preference. It also suggests that individuals may experience different benefits of the same content, highlighting the importance of consideration of individual differences.

There were also differences between participants in terms of those who did and did not report mood change in response to the intervention, as well as those who would and would not attempt to modify their own mood independently in the future. For instance, some participants reported being happy enough at baseline, and therefore the mood enhancement intervention was unnecessary. Whilst a ceiling effect is possible, one alternative explanation for this is that older adults may be more concerned with

maintaining mild positive emotional stability as opposed to intensifying positive emotions. For instance, Carstensen, Isaacowitz, and Charles (1999) argue that as people age they go through emotional development, resulting in several changes including an increased focus on stable positive moods. This may be due to better emotional regulation (Gross et al., 1997), or a shift in goals, away from the long-term, and towards achieving emotional satisfaction in the present (Carstensen, Fung, & Charles, 2003). This may then be reflected in older adults' activities, social groups, and indeed, film and television preferences (Mares, Oliver, & Cantor, 2008). Some participants similarly reported that they were already in a bad mood at the start of the intervention, due to either personal reasons or due to anxiety surrounding the study procedures, i.e. having blood taken and receiving the vaccine. According to the stress-buffering model of positive affect (Chapter 5, Section 5.3), increased positive mood may enhance immune response to influenza vaccination by reducing the impact of stress. Therefore, it may be expected that those who were stressed or anxious at the beginning of the intervention would have benefited more from positive mood enhancement, in line with findings from exploratory analyses described in Chapter 7. Results from this qualitative study, however, suggest that for some participants reporting a negative mood at the beginning of the study, this may have prevented the intervention from working. Thus, whilst not necessarily contradicting the theory, this does suggest that a simple video-based mood enhancing intervention may not be sufficient to benefit individuals with perceived high pre-intervention negative mood or stress.

There were several aspects of the study experience itself that may have impacted on participants' mood outside of the intervention, including the

environment, which was perceived as calmer and more personal than standard flu clinics, the group format, and feeling helpful as a result of taking part. These aspects may have further contributed to the study being a positive experience, and potentially to improved positive mood. This suggests that the very act of taking part in research may contribute to intervention effects. Indeed, several reviews have demonstrated that answering research questions, taking part in research interventions and engaging with research activity can impact participants (French & Sutton, 2010; McCambridge et al., 2011; McCambridge & Kypri, 2011; McCambridge et al., 2014).

Participants in both intervention arms identified benefits of receiving choice, including both increase in personal relevance and increased control. This supports previous research outlined in Chapter 4, demonstrating relationships between choice, control and preference in terms of a variety of improved outcomes, such as motivation and interest (Cordova & Lepper, 1996) and clinical outcomes (Lindhiem et al., 2014). However, the findings of the present study suggest that the very act of being given choice may not necessarily be sufficient to enhance perceptions of mood, as suggested by some of the participants who received choice but reported that they did not enjoy the content. Thus, choice alone may not be enough to improve mood over a no-choice equivalent, particularly in cases where the options available do not increase personal relevance or control, as the available options are not liked. This is consistent with results from the randomised controlled study in Chapter 6, demonstrating no significant differences between the two positive mood interventions in terms of positive mood outcomes. Also interesting to note is that attitudes towards the options available to choose between appear to be a determinant of whether choice is perceived as beneficial or not, suggesting

that no-choice interventions may be as effective as choice interventions in circumstances where preferences match what is received. This is consistent with meta-analytic evidence demonstrating significantly better treatment outcomes, particularly in terms of mental health and mood, but also in terms of physical health and behaviour change, in patients matched to their preferred treatment, compared to those not matched to their preference (Delevry & Le, 2019; Swift & Callahan, 2009; Swift, Callahan, Cooper, & Parkin, 2018). As well as better clinical outcomes, preference matching is also associated with increased treatment initiation, adherence, and reduced drop-out. In fact, Swift et al. (2018) found that those who were not matched to their preferred treatment were almost twice as likely to drop-out.

As well as the benefits of choice, participants did identify some negative aspects, such as the potential for too many options being overwhelming, and too few choices resulting in no desirable options, both of which may in fact result in more negative consequences than just not receiving choice at all. This is supported by research showing a too-much-choice effect which may lead to choice deferral, decreased motivation and satisfaction, and increased regret (Botti & Iyengar, 2006; Haynes, 2009; Iyengar & Lepper, 2000; Reutskaja & Hogarth, 2009). This also supports Patall et al. (2008) who found choice interventions to be more effective for motivation when participants were provided with between three and five options, as opposed to only one option or more than five options. Thus, this demonstrates the importance of providing the right number of options to choose between.

Whilst the provision of choice was reportedly liked by participants in the choice group, and desired by some participants in the no-choice group, it is worth noting that this may have been influenced by several factors. For instance participants who were given choice may be more likely to report positive outcomes due to a sense of responsibility for the consequences of that choice, and thus a potential cognitive dissonance if that choice does not have a positive outcome (Festinger, 1962; Goates-Jones & Hill, 2008). Another aspect to consider is that those in the choice group were not expecting choice, and those in the no-choice group did not know that they were receiving a more limited version of the intervention. This differs to situations where choice may be expected, or there is a knowledge of alternatives, such as when selecting a treatment for a physical or mental health condition. Therefore, it is possible that choice may be more beneficial, or conversely no-choice may be more detrimental, in situations where choice is expected, or specific options are desired (e.g. Bradley, 1997; Brewin & Bradley, 1989; McPherson & Britton, 1999). Finally, there may be individual differences within participants that influence the impact of receiving choice. For instance, it has been suggested that the benefit of choice may depend on individual factors such as desire for control (Burger & Cooper, 1979), with those with a higher desire for control having greater benefits of choice compared to those with lower desire.

Overall, these findings suggest that there may be multiple elements influencing the effect of the intervention on both mood and immune response. The specific intervention content, the study process itself, the provision of choice and existing beliefs regarding mood and influenza vaccination may all contribute to mood enhancement. These findings suggest that there is a wide amount of variation and individual differences within the older adult population

in terms of these factors, which further emphasises the need for, and value of, choice in such interventions.

8.5.2 *Optimisation of the intervention and study experience*

Both thematic and content analysis identified aspects of both the interventions and the overall study experience that work well in their current form, as well as some that could be improved upon in future iterations. In terms of the choice intervention itself, the majority of the participants found the number of choice options available to be about right or made no comment on the number of options. As mentioned above, this is in line with previous research demonstrating that choosing between three and five options may be optimal for motivation, with the For-ME choice-based intervention involving three separate choices, and suggests, in line with the perception of majority of participants, that this does not need to be changed. Based on content analysis, the majority of participants did not identify other intervention content ideas. Further, given that both interventions were shown to significantly improve mood (see Chapter 6), despite the content being somewhat limited, this suggests that both interventions were still effective overall. Additionally, when developing future iterations of the choice intervention, the number of video clips does not need to be expanded, particularly considering the importance of balancing a variety of clips to suit the majority of participants, whilst not including too much choice as to overwhelm participants.

Several aspects regarding the overall study experience were discussed by participants when considering what worked well and what could be improved. For example, the analysis revealed that there was quite a large amount of

variation between different GP practices in terms of facilities, as well as the degree of participant interaction. This may warrant further consideration for future trials, given that these variations may have led to differential impacts on participants' moods at the time of the intervention. On the other hand, variation between sites is to be expected when carrying out multi-site research, and is also reflective the variation in GP practices in real-world settings, thus making results of this research more applicable to the real world.

Most participants acknowledged that although not necessarily the most comfortable or welcoming of environments, a clinical setting was required given that clinical activities were being done as part of the study. However, whilst a clinical setting was expected by participants, this did not have to come at the expense of a friendly atmosphere. Many participants suggested that one way in which to create such an atmosphere in a clinical setting could be the provision of refreshments. Whilst this may have practical implications in terms of facilities and time, potentially resulting in less participants seen per day, the benefits may include creating a more relaxed, friendly environment that aids social interaction with other participants. Indeed, many participants enjoyed the group aspect of the intervention sessions, and some indicated that this could be further exploited by promoting social interaction, for instance by introducing participants to each other at the very start of the session. This may have the additional benefit of promoting a sense of social inclusion, and reducing social isolation, an issue that is prevalent in older adults and related to poorer immune response to vaccination (e.g. Moynihan et al., 2004). Thus, this may result in the wider study experience contributing the mood enhancement, rather than the intervention alone. This is caveated by the fact

that some people may prefer one-to-one interaction, and so enhancing the group element may not be beneficial for all, although would not necessarily have a negative effect. Additionally, whist some participants were happy for sessions to be longer than the designated hour, others reported preferring the quicker in-and-out approach of usual flu vaccine clinics. Thus, the potential benefits of a longer, more social study experience would need to be balanced against both the implications in terms of time and facilities, and the preferences of all participants. These findings may also suggest that as well as choice regarding intervention content, choice in terms of intervention context and environment may also be important, given the observed individual differences.

Whilst these aspects are important to consider, it is also worth noting that most participants described the experience as pleasant and well-run, and over a third identified no ways in which the experience could be improved. This is in-line with results from the randomised controlled trial presented in Chapter 7, indicating that both interventions resulted in improved mood, and showing that in all three groups, mood was high at pre- and post-intervention assessment.

8.5.3 *Strengths and limitations*

This qualitative study has several strengths. For instance, a common problem in qualitative research is that often participants are self-selecting, which may mean that those particularly motivated to voice an opinion, i.e. those with extremely positive or negative experiences are more likely to take part. This was avoided in the current study, using an approach that involved purposively inviting participants from a random selection of those who had participated in

the randomised trial. Despite the random selection, not all GP practices are represented by the participants, which may mean that not all experiences and views are represented. However, from the random sample, participants were purposively selected according to GP practice to try to ensure that the participants proportionally reflect those taking part in the randomised trial. As such, the three GP practices not represented in this study comprised 0.9%, 1.3% and 3% of the total number of participants, and thus this study reflects the vast majority of the randomised trial participants.

Additionally, and in accordance with PPI input, the timing of the interviews was considered, and were carried out as soon a possible following the study visits. This was to ensure maximum recall and increase the likelihood that participants' reported experiences and reflections were as accurate as possible. Further, the fact that the same interviewer conducted all interviews meant that the approach to questioning was consistent, and responses to interview questions were not influenced differentially by characteristics of the interview. For example, research has shown that certain characteristics such as gender, can influence interactions between the interviewer and respondent (Matteson & Lincoln, 2009). The involvement of a second researcher to discuss theme identification and development was also a strength of this study. This meant that themes were not developed in isolation and benefited from additional insight and perspectives from someone not as involved in or as immersed in the data.

Finally, it should be acknowledged that such qualitative work is not common, despite the potential benefits of understanding participants' experiences and

perceptions of the research they are involved in. Therefore, the fact that this study was conducted in the first place, is an acknowledgement that there is little understanding currently as to how mood enhancing interventions might work and represents the first step in trying to understand this using participant insight. Despite the challenging nature of attempting to access participants' perceptions of the potential processes and mechanisms, this research has identified several potential mechanisms through which the intervention may improve mood and indicates that the relationship between improved mood and immune response is subconscious. Both of these represent valuable and novel insight which would not have been gained without this qualitative study, and may inform future work in this area.

There are also a number of methodological issues that should be considered when interpreting these findings. Firstly, the findings discussed here may reflect limitations in the construction of the interview schedule. For instance, participants were only asked about specific mechanisms and processes relating to the intervention, and not about other factors that may affect how well the intervention or vaccines worked. Therefore, discussions may have been limited by the questions asked, or the way in which they were asked, with resulting discussions unable to penetrate far enough to understand other potential mechanisms that may have also been influential in how the intervention exerted (or did not) its effects. The use of an iterative approach to the interview schedule development may have mitigated this limitation, and would be recommended for similar work in the future.

Secondly, and as with all qualitative research, there is the possibility of researcher bias and the influence of the researcher's own beliefs and assumptions on the data and analytic process. However, every effort was made to ensure that any potential biases were minimised. For example, the development of the interview schedule was based on feedback with both a PPI group and through discussion with two other researchers involved in the study. A reflexive diary was kept allowing the researcher to reflect on their own beliefs and the potential impact of this on the research. The transcripts were analysed once all interviews had been completed to ensure that the researcher was not influenced by subconsciously developing themes based on the data. Thematic analysis adopted an inductive approach to ensure that the themes and subthemes were true to the original data and therefore representative of the participants' views. Further, themes and subthemes were discussed through an iterative process with another researcher to review, revise and refine all themes.

Finally, the findings of the study discussed here are also crouched within the context of the perceptions and views of the participants, rather than reflecting a truly accurate and definitive account of both mechanisms and experiences of the intervention. Thus, the findings should be interpreted with this in mind.

8.5.4 *Considerations*

There was variation in terms of the degree of insight participants reported in terms of the potent factors regarding the perceived effect of the intervention. Whilst some participants appeared to identify such factors readily when asked why the intervention did or did not impact their mood, others struggled to pin-point the specific mechanism or feature of the intervention that resulted in their

experienced effect. This is particularly true for participants who did not have strong feelings regarding the intervention, i.e. they neither really enjoyed nor really disliked the experience. Some participants noted that they had not previously considered this, perhaps because it was not viewed as a significant experience for them. Alternatively, the difficulty experienced by some in identifying how and/or why they perceived the intervention to work (or not), may reflect that the processes underlying the link between the intervention and the impact on mood is subconscious, and thus difficult to tap into. As previously noted, this may also be a result of the structure of the interview schedule, and the specific questions and prompts asked.

In terms of the underlying processes linking improved mood with vaccine response, most participants struggled to comment. For instance, some described how their mood had changed as a result of the intervention, but not the impact that they thought this may have on the outcome of the vaccine. Many participants reported that the intervention did not have any influence on their vaccination, with some sceptical of a link between mood and vaccine response, which were seen as distinct processes. This suggests that amongst the public, the biomedical model of health, as opposed to the bio-psycho-social model, has dominance. A small number of participants felt that positive mood would be beneficial to the effectiveness of the vaccine, with some citing a link between being a positive person and having positive outcomes more generally. From an interviewer perspective, this was also reflected in the difficulty in getting participants to reflect on this relationship and potential mechanisms involved. Participants often needed to be asked several times, or asked to expand on their responses to reflect on this relationship, with many struggling to access any reflections. Together, this again suggests that the link

between mood and vaccine response is difficult to tap into for many participants, and that they struggle to provide insight into this relationship. Again, this may further be confounded by unexpected difficulties created by the interview schedule, which may not have asked the right questions, or asked them in the right way to access such insights.

When asking participants about aspects of the intervention and study that could be improved upon in the future, many participants again struggled to answer, however this is more likely reflective of the fact that many participants found the study to be suitable as it was and therefore did not have much to say. Unlike questions regarding potential underlying processes and mechanisms, all participants seemed to easily understand and respond to questions regarding optimisation, even if this was just to say that there was nothing that they would change. Thus, this suggests that participants are able to identify aspects of an intervention they do and do not enjoy, and that limited responses may reflect the fact that the study was generally well-received, and not an extensive or laborious experience.

8.5.5 *Implications and future research*

This study has identified several possible mechanisms through which a brief positive mood intervention enhances mood, and may subsequently impact vaccine response. It has also contributed to the understanding of how best to operationalise a future definitive trial, including aspects participants reportedly liked and would improve upon in the future.

Results from this study suggest that both interventions are acceptable to participants in their current formats, and that the study was generally well run and well-liked by participants. However, consistent with the results of the RCT outlined in Chapter 6 and analysis in Box 8.2, potential ceiling and/or floor effects may be at play. Therefore, future iterations of the intervention may benefit from targeting participants who were not already either very happy or had low mood at baseline, and thus have the greatest opportunity to improve.

In terms of potential participant-identified mechanisms and processes underlying the link between the interventions and mood, and potentially vaccine response, there are several implications of the current study. Firstly, the present interventions mainly focused on enhancing high arousal positive affect, which is consistent with results from Chapter 6 indicating that levels of arousal increased from pre- to post-intervention in both intervention groups. Findings from this qualitative study suggest that some participants may prefer low arousal content, and being in low arousal positive moods. Additionally, some participants may experience low arousal positive mood in response to high arousal content. There is currently very little research on the effect of low arousal moods on the immune system, and influenza vaccine response specifically. Therefore, this avenue warrants further investigation, with future studies investigating the impact of low arousal positive mood enhancement immediately prior to influenza vaccination, for example.

In terms of intervention content, whilst there were differences in participant opinions, both the results of this study and the findings of the RCT indicate that both interventions improved positive mood effectively, therefore may not

need to be adjusted further for a future trial. Similarly, whilst there were some differences in attitudes towards choice, overall, results from this study supports findings from the RCT, demonstrating no significant differences between the two interventions in terms of positive mood outcomes. Thus, a future definitive trial may want to use either version of the intervention, as these should produce similar results.

8.6 Chapter summary

The qualitative study outlined in this chapter set out to explore the experiences of 17 participants in the randomised controlled trial described in Chapters 5-7. In doing so, it aimed to understand participants' perceptions in terms of how and why the two positive mood interventions did or did not work in terms of both the relationship between the two interventions and mood, and how this may impact vaccine response. It also aimed to identify ways in which the intervention and study experience as a whole may be further optimised. Findings suggest that overall, both interventions were well received by participants, as was the study experience. Several potential mechanisms underlying the link between the interventions and mood were identified. Findings regarding the two interventions were consistent with findings from Chapter 6, indicating that both were equally effective in enhancing positive mood and suggesting that further adjustment may not be necessary. Several potential avenues for improving the overall study experience were also identified as areas to consider for a future definitive trial. In the next chapter, the entire programme of work presented in this thesis will be considered, and the implications of this will be discussed.

9 Chapter 9: Overall discussion

9.1 Chapter overview

This chapter aims to provide a brief overview of the systematic review with meta-analyses, the randomised controlled clinical trial, and the qualitative interview study. The implications of these studies and their findings will be discussed, and some reflections regarding the challenges faced when conducting the research, and recommendations for the future will also be considered. Finally, potential areas of future research will be highlighted.

9.2 Introduction

The main aim of this thesis was to optimise a previously trialled positive mood intervention, assessing the effectiveness of both a novel intervention involving active participant choice compared to a standardised fixed-content intervention. It also aimed to explore whether these positive mood interventions could enhance influenza vaccine response in older adults, in terms of antibody response. Chapter 1 set out to provide the context for this work, including the importance of vaccinations, and the issue of reduced response to influenza vaccination in older adults compared to their younger counterparts. Whilst the development of more effective vaccines is important, it is a very long and costly process (Andre, 2002; Gouglas et al., 2018; World Health Organization, 2013). Thus, Chapters 2 and 3 explored the evidence base for the relationship between vaccine response and several modifiable psychological factors, which offer opportunities for increasing vaccine effectiveness comparatively quickly and cheaply. These chapters culminated in outlining the body of prior work within which this thesis is set, including a randomised controlled trial of a brief positive mood intervention. Chapter 4 built on this by examining whether the provision of choice may be used to

further optimise the previously tested positive mood intervention, by presenting a comprehensive systematic review and meta-analyses of choice-based versus no-choice interventions in terms of mood and retention-related outcomes. Chapters 5-7 went on to describe the development, design, analysis and results of a three-arm randomised controlled clinical trial, comparing the previously tested positive mood intervention, to both a new choice-based intervention and usual care. Following the results of the trial, Chapter 8 then went on to describe a qualitative study carried out with a selection of participants who had taken part in the trial, to capture their perceptions of why the intervention did or did not work for them in terms of both mood and vaccine response.

It is worth noting that whilst the studies comprising this thesis are presented in a linear manner, the reality is that the research process is rarely so clean. Due to time constraints surrounding the development of the intervention and applying for ethical approval for the trial, it was necessary to begin developing the intervention before the systematic review and meta-analyses were finalised. Instead, the selection of choice was informed by an initial scope of the literature which suggested that choice may be beneficial in a range of contexts.

Together, these studies acted as the next step of development of positive mood interventions aiming to improve mood immediately prior to influenza vaccination in older adults, with the overarching goal of improving vaccine effectiveness in this vulnerable population. This chapter will discuss the various implications of these study findings, before reflecting on some of the

key challenges and considerations for positive mood intervention development and trialling. Finally, the possibilities in terms of the next steps for research, building on the knowledge gained in this thesis will be outlined.

9.3 Clinical implications

The results of the studies presented in this thesis have several clinical implications. Results of the systematic review suggest that clinicians, and researchers, should consider the provision of choice to patients, particularly if there are concerns regarding retention or adherence to a treatment plan or intervention. Whilst results from the review for mood outcomes were inconclusive, given the lack of associated harm, clinicians may also want to consider the provision of choice in these contexts. Patient choice is being increasingly advocated for, with the rise of public and patient involvement and the steady move away from more prescriptive consultation styles. Previous evidence has indeed shown benefits of matching interventions or treatments to patient preference, shared decision making and choice (e.g. Lindheim et al., 2014). The results of this review complement and add to this body of research, demonstrating, through the stringent inclusion criteria, that these beneficial effects are in fact due to the element of choice alone, rather than other aspects such as the influence of the clinician, the varying comparison groups and the specific interventions or treatments on offer. Further, this review also demonstrates that choice can work in most contexts, given the wide range of interventions included, yet minimal evidence of heterogeneity in the meta-analyses in terms of the influence choice has across those interventions. The fact that the review found no real differences between different types of choice, the number of choice opportunities, or number of options provided per choice opportunity, in terms of their effects on the

studied outcomes, also suggests that choice could be operationalised in any way, making the inclusion of choice in clinical settings relatively straight forward and easy to implement.

The randomised controlled trial demonstrated that both positive mood interventions were able to improve mood significantly more than those in the usual care group, in a population with already high levels of positive mood. Therefore, for an older adult population with lower baseline levels of positive mood, the potential benefits are even greater. Given the well-documented benefits of positive mood for a range of health conditions and clinical contexts, the potential implications of this finding may also extend beyond that of older adults receiving their influenza vaccination, in terms of other brief medical encounters or treatments that may benefit from mood enhancement. For instance, positive mood has been associated with increased pain thresholds (Tang et al., 2008; Weisenberg et al., 1998) and reduced self-reported symptoms in a range of conditions (Cohen et al., 2003; Sullivan, LaCroix, Russo, & Walker, 2001). Results from the For-ME trial also showed that the interventions significantly reduced negative affect compared to usual care. The implications of this are similarly wide, with negative moods associated with a range of negative health outcomes, including slower wound healing (Christian, Graham, Padgett, Glaser, & Kiecolt-Glaser, 2006), poorer surgical response (Rosenberger, Jokl, & Ickovics, 2006) and lower pain tolerance (Weisenberg et al., 1998). Therefore, positive mood enhancement may offer benefits in a number of different patient groups and contexts, including before surgery, brief potentially painful procedures, and biopsies, to name a few examples.

Whilst the results of the trial did not show significant differences between groups in terms of antibody response, despite intervention groups having significantly higher improvements in positive mood, discussions of the evidence have argued for a number of factors that may account for the null results. Thus, whilst the importance of mood at the time of influenza vaccination remains unclear, it should not be written off prematurely, given prior evidence. Clinicians should still consider their patients' mood at the time of vaccination and be aware of the potential for a benefit of positive mood on vaccine effectiveness. They may want to consider low cost and low effort strategies to improve the general experience of influenza vaccination, such as the waiting room environment or atmosphere, the latter of which was identified by several participants as important during qualitative analysis. These are examples of simple ways to improve mood with few downsides, but possible benefits for vaccine efficacy.

Alternatively, as influenza vaccines may, through the development of new adjuvants and stronger doses, get more effective to the point where any benefits of positive mood enhancement may no longer be observable, clinicians may want to consider the potential benefits for other populations and vaccinations. This includes other vaccines where effectiveness may be impacted by age and/or other factors associated with immune system disruption, or populations such as young, healthy adults. Indeed, whilst the evidence presented in Chapters 2 and 3 focused on influenza vaccine in the older adult population, where evidence was lacking, research focusing on other populations and vaccinations was highlighted. This evidence demonstrated how both stress and negative affect have been implicated in the effectiveness of vaccines including the hepatitis B vaccination series and a

novel antigen keyhole limpet hemocyanin, in student populations (Glaser et al., 1992; Marsland et al., 2001; Smith et al., 2004). Despite being different vaccines and populations, the specific impacts of the various psychological factors on immune parameters remain similar to those impacted by positive affect, suggesting that these other populations and vaccinations may also be impacted by positive affect. Similarly, other populations with compromised immune functioning who may be vulnerable to vaccine failure may also benefit from the present intervention. For instance, individuals with HIV have been shown to have an increased hospitalisation and mortality risk due to influenza (Lin & Nichol, 2001; Neuzil, Reed, Mitchel Jr, & Griffin, 1999), whilst also exhibiting poorer response to vaccination (Zanetti, Amendola, Besana, Boschini, & Tanzi, 2002). Other populations with an increased risk of severe outcomes but a reduced vaccine response include those with obesity (Neidich et al., 2017) or other immunosuppressive illnesses (Kimball, Zhu, Wyatt, Trabue, & Talbot, 2021). Therefore, clinicians may also want to consider the potential impact of positive mood before administering vaccines in a range of clinical scenarios.

9.4 Theoretical implications

The studies described in this thesis were not set up to formally test a specific theory or model. However, two models of positive affect and the immune system were briefly outlined in Chapter 5 whilst discussing how the positive mood interventions may work in terms of effects on the immune system. To recap, these included the main (direct) effects model and the stress-buffering model. The main (direct) effects model postulated that trait positive affect may influence immune functioning through several mechanisms such as health practices and autonomic nervous system activation, whilst state positive affect

may impact cortisol and endogenous hormone levels. This is not supported by the findings of this thesis, in which exploratory analyses found no relationship between trait positive affect and immune outcomes, although it is worth being cautious in this assertion as the For-ME trial only assessed one measure of immune function, vaccine specific IgG antibody responses, which itself is a downstream parameter that is influenced by a cascade of immunological processes that occurred over a period of weeks following our initial intervention exposure. We therefore cannot know from this study whether other, more proximal immune parameters were impacted by positive mood and/or how long lasting these effects were. Mediating factors such as cortisol, adrenaline and noradrenaline were not assessed in the For-ME trial, therefore support for this part of the model could not be determined.

The stress-buffering model (Pressman & Cohen, 2005) suggests that positive mood may enhance immune response by reducing the negative impact of stress. Thus, according to this model, those with high stress levels may be expected to demonstrate the greatest benefits of mood enhancement. Whilst those with the highest levels of stress saw a significantly greater increase in positive affect from pre- to post-intervention compared to those with the lowest levels of chronic stress, regression analyses found no relationship found between stress scores and antibody levels. However, it is interesting to note that when a tertiary split analysis was done, those with the highest stress had non-significantly higher antibody level scores (based on point estimates), providing limited support for this model.

9.5 Methodological implications

As previously stated, the results of the systematic review presented in Chapter 4 indicated that there was a significant benefit of providing participants choice in a range of contexts. As well as implications for clinical practice, there may also be implications for research methodology. In the For-ME study, participants were given choice of intervention content: they could make three consecutive selections of videos from four categories, each with three options, thus they could select three from a total of 12 video clips to watch. Whilst the review suggested that the way in which choice is offered may not be important, results of the qualitative study highlighted that not only were there individual differences between participants in terms of preferences of video content, but there were also differences in terms of preferences regarding aspects of the study design, such as group versus one-on-one settings, and whether the standard flu clinic approach (which was much quicker) was preferred. Therefore, when designing choice interventions, incorporating a range of types of choice may be preferable, for instance offering a choice of study group, or settings for instance, as well as choice of intervention content. To make such a study realistic and manageable, this may be best operationalised in a trial within trial design, or a design where only those with no strong preferences in terms of group or setting are randomised.

As well as operationalising choice within an intervention to improve outcomes and retention of participants, it is possible that choice may also have utility in terms of aiding the recruitment and retention of study sites. Studies of barriers to participation in research in the primary care context have cited concerns regarding not having a voice in the research process, as well as practical barriers such as a lack of time and resources (Brodaty et al., 2013; Hummers-

Pradier et al., 2008). The provision of choice has the potential to address both of these barriers, by giving practices more control in research activities, and by potentially allowing them to choose procedures and/or approaches that reduce the burden on the practice.

A consideration that was made during the design stage of the randomised controlled trial was the best method of assessing state mood. Ultimately, three measures of state affect were included: one that had been used in the previous feasibility study, one comprising an adjective list, and one specifically designed as a non-verbal assessment of mood for digital platforms. Whilst these measurements ensured that both positive and negative affect valence and arousal were captured, and that both word and pictorial methods were used, there are still some concerns with these types of subjective, one-off ratings of mood. Whilst compared to trait measures of positive affect, state measures are more accurate and are less likely suffer from issues like recollection biases, they are still vulnerable to issues such as self-presentation bias or variation in response styles (Pressman, 2019). Alternative methods of assessing state affect may include objective assessment of mood through, for example, expression of naturally occurring smiles whilst watching the intervention content. Naturally occurring smiles during qualitative interviews have previously been associated with health outcomes (Davidson, Mostofsky, & Whang, 2010; Fredrickson, 1998), demonstrating precedent for this type of objective measure being associated with biological processes. One potential operationalisation of such an approach in a study utilising a positive mood intervention such as the ones used in the present thesis, could be the inclusion of a camera on the device on which participants watch the intervention content, which is then analysed using facial expression

recognition software. Alternatively, and less costly (though more subjective), a behavioural coding approach could be implemented.

9.6 Reflections, challenges and recommendations

Throughout this thesis, the various strengths and limitations of each study have been discussed in detail. This section focuses on some reflections regarding more general challenges faced when carrying out the research, as well as recommendations to be considered if the work were to be repeated, or for a future definitive trial that would be on a much larger scale.

9.6.1 *Usual care arm*

The treatment of the control arm was considered whilst designing the For-ME trial, and there were several concerns regarding the most suitable approach. The primary difficulty with this group was that the nature of normal flu clinics, in which patients may be given a timeslot but these are often not kept to, may take place at alternative locations, and are generally very quick, meant that it was impossible to replicate this in a trial setting. As an example, simple study procedures such as obtaining informed written consent introduces an activity that is not part of usual care and increases the duration of the appointment. Additional factors, including being given a booked appointment, being seen in small groups, and completing mood assessments, whilst necessary, were further deviations from usual care. Usual care participants were also matched in time to the active interventions, further extending the duration of the appointment. Whilst this was deemed necessary to ensure that any benefits seen in the intervention arms over the usual care arms were not due to factors such as attentional bias or differences in the setting, the by-product of this

decision was that it became much longer than a standard flu clinic appointment.

The initial plan for the usual care arm was to have participants in this group stay in the waiting room, in order to simulate a routine GP visit as much as possible. However, it became clear early on that this was not always feasible. For instance, due to GP practice layouts, waiting rooms were sometimes on a different floor, or very far away from the room that had been allocated as the session room. Thus, it was difficult for researchers to be on hand to participants in the waiting room in case there were any questions or issues with the instructions or tablet devices, whilst also being available to participants waiting to go for their blood sample. Additionally, this process sometimes caused confusion for participants at the end of the 15-minute wait, if the researcher was not present. Finally, there were some problems with waiting room capacities, where it was not possible to have all study participants in the waiting room along with patients attending normal GP appointments. Thus, the decision was made early on to have participants in the usual care group carry out their 15-minute waiting period in the study room with other participants.

Together, these factors mean that the usual care group may not have represented a realistic usual care setting, and may be more representative of an attention matched ‘no treatment’ condition. Future studies should consider the treatment of the usual care group, and decide where compromises need to be made in order to balance capturing a true usual care condition with practical considerations and desire to minimise bias. Such studies may want

to consider the use of cluster designs, which may give the most accurate measure of usual care, particularly if consent is obtained in advance so as not to interfere with usual vaccination care.

9.6.2 ***COVID-19***

The COVID-19 global pandemic represented an unprecedented and particularly difficult challenge that occurred approximately one and a half years into this programme of research. Fortunately, at the time of the first national lockdown, the majority of data had been collected: all study visits had taken place and qualitative interviews had been conducted. As briefly outlined in Chapter 5, the pandemic and associated closures of Universities resulted in a substantial delay to analysis of blood samples in the laboratories, and upon recommencement a number of procedures related to the analyses were altered, due to new safety policies and a shift in the laboratories research priorities. These closures also meant that other immunological work using collected samples and follow-up studies during the PhD were not possible.

Whilst the onset of a global pandemic could not be predicted, there are a number of lessons that could be learnt and implications of the pandemic on future research. For instance, the uptake of safety behaviours, such as increased hand washing, mask wearing and social distancing meant that influenza activity was extremely low during the 2020-2021 influenza season (Public Health England, 2021b). This shows how effective these simple measures are at reducing influenza illness. Focusing on retaining such behaviours during future influenza seasons therefore may be a more effective mechanism through which the serious consequences of influenza in the older

adult population can be reduced, compared to focusing on making vaccinations more effective. Alternatively, given that modelling for the 2021-2022 influenza season predicts that influenza activity could be up to 50% larger than typically seen (Department of Health & Social Care, 2021), quick and easy ways to improve vaccine effectiveness in vulnerable groups, alongside promotion of previously mentioned safety behaviours, may be necessary to negate the negative impacts of influenza. This highlights the importance of the continuation of research aiming to improve vaccine efficacy relatively quickly and cheaply.

A further implication of the pandemic on the future direction of this research surrounds the group setting approach to the study. Participants viewed their interventions on individual tablets, but in groups of up to eight. The findings from Chapter 8 noted that this social element of the trial was particularly well liked by participants, and was highlighted as something that may be further exploited in future trials, as a tool to enhance mood even further. Additionally, section 9.3 noted some benefits of group settings and shared experiences in the context of comedy and of older adults. However, the COVID-19 pandemic raises concerns regarding the safety of this approach. Airborne transmission appears to be one of the main routes through which the virus is spread, meaning that coughing, sneezing, talking and laughing in close proximity to others may cause infection (Centers for Disease Control and Prevention, 2021a; Peng et al., 2020). As a result, measures such as social distancing and restrictions on social gatherings have been used to mitigate the spread of the virus (Mahase, 2020; Singh & Singh, 2020). Therefore, incorporating a social element into the present intervention may not be appropriate whilst COVID-19 continues to be prevalent, particularly in the older adult population,

who are at a greater risk for more serious consequences of COVID-19 infection (Zhou et al., 2020).

The studies presented in this thesis may also have implications for COVID-19 vaccines. Whilst there is no evidence of reduced vaccine efficacy in older adults (Heath et al., 2021), given both the high transmission rate and severity of the illness, as well as its impact on the NHS and its staff (Ge et al., 2020; Gemine et al., 2021), maximising their effectiveness is of significant importance. The pandemic has been associated with an increase in a range of psychological factors associated with poorer response to a range of vaccines, including depression, stress, and loneliness, as well as behavioural factors including reduced physical activity, increased alcohol consumption and poorer sleep (Madison, Shrout, Renna, & Kiecolt-Glaser, 2021), thus the need for improved vaccine effectiveness is even greater. There is currently no evidence for the role of psychological factors on the effectiveness of COVID-19 vaccines. However, given the low cost, resource use, and lack of requirement for specialist training to deliver, psychological interventions prior to COVID-19 vaccination should be explored as a potential way to boost their effectiveness. The potential benefit does not stop at initial vaccination. Evidence suggests that immunity gained following the COVID-19 vaccine starts to wane over the six months following vaccination (Levin et al., 2021). Therefore, investigating whether psychological factors can not only impact initial vaccination, but also subsequent doses including boosters, and whether there are impacts on the duration of gained immunity, are all important questions and directions worthy of investigation.

9.7 Future research

As noted in Chapter 4, there are several ways in which a brief positive mood intervention may be optimised. For the For-ME study, the provision of choice was selected, however alternative methods may be more effective in enhancing mood. Whilst these were rejected on the grounds of impracticality in the primary care context, it is possible that they may be feasible in other contexts. For instance, a group-based intervention may be suitable in a care-home setting, where residents could watch the intervention together before attending an in-house vaccination clinic. Indeed, research suggests that group contexts can intensify emotions, including both sadness and happiness (Shteynberg et al., 2014), and increase the frequency of laughing, compared to when alone (Provine, 2004). Group-based interventions may also have additional benefits, including enhanced wellbeing as a result of taking part in shared social activities, particularly for older adults living in care facilities (Haslam et al., 2010). Therefore, the benefits of such interventions in this population may be two-fold. Alternatively, as discussed in section 7.3.1, it may be that methods other than participant choice to select intervention content may be more effective, such as a trained coach, or individualisation based on prior assessments of participant preferences.

Similarly, both of the trialled interventions were designed to improve positive mood using 15 minutes of video clips, consisting of primarily comedy and music. Thus, the impact of other methods of positive mood enhancement in this population is unknown. Previous research in primarily student populations has shown evidence of a variety of immunological changes following hypnosis (Zachariae et al., 1991), writing about humorous films (Njus et al., 1996), and reflections of happy personal experiences (Hucklebridge et al., 2000). Whilst

hypnosis does not lend itself well to primary care, a brief writing or reflection intervention may be feasible, and therefore may warrant further exploration. Additionally, in a meta-analysis of mood induction procedures, Westermann, Spies, Stahl, and Hesse (1996) explored the effectiveness of a range of approaches to inducing positive mood, ranging from films/stories or music, to social interaction or positive feedback following a task. The largest effect was seen for procedures involving film/story plus an instruction to imagine the situation and the feelings suggested, followed by film/story alone. Whilst it is unclear whether these procedures result in immune changes, both are easily applied to the older adult population and the primary care context, therefore should also be explored.

Chapter 7 also identified and discussed in detail several avenues for future research on the basis of the immunological findings of the randomised controlled trial. For instance, in relation to the uncertainty surrounding how a positive mood intervention might impact immune functioning, a series of mechanistic studies were proposed aiming to determine (i) what, if any, other immune parameters are impacted by increases in positive affect, (ii) how long are any changes in immune parameters sustained for, (iii) is a 15-minute intervention sufficient to cause such changes to immune parameters, and (iv) how long after positive mood enhancement should vaccination occur. The results of such studies would be able to inform further intervention development to ensure that not only is the intervention optimised in terms of positive mood, but also in terms of maximising the potential for mood improvements to translate to clinically meaningful changes to immune function.

These mechanistic questions may be answered by several individual studies. For instance, study one may be an observational study in which older adults watch either the standard fixed-choice or choice interventions (as both appear to be equally effective at enhancing positive mood) and have blood samples taken at baseline and immediately post-intervention to assess a range of immune parameters and determine which (if any) respond to mood enhancement. A second observational study may involve a repeated measures design where blood samples are taken at baseline and then at regular intervals from immediately post-intervention to up to 12 hours post-vaccination. This would inform whether or not there is likely to be a wearing-off effect between the end of the intervention and the point of vaccination, and if so, the maximum amount of time that can elapse before effects start to decline. A third study would aim to assess different intervention durations, by comparing the effect of a 15-minute intervention with one that has similar content but is 30 minutes, on the immune parameters identified in study one. Lastly, a two-armed study where one group receive the intervention before vaccination and is compared to a group who receive the intervention after vaccination in terms of immunological response, would address the question of whether post-exposure vaccination is more effective than pre-exposure vaccination, as seen in the stress literature (e.g. Miller et al., 2004).

Following the mechanistic work, once questions regarding duration, timing and outcomes have been addressed, a large-scale definitive trial should be conducted, powered based on the immunological outcome identified in the mechanistic studies or clinically relevant outcomes such as the number of doctor visits relating to influenza, prescriptions for upper respiratory illness, hospitalisations, pharmacy visits, self-reported influenza illness or clinically

confirmed illness. Such outcomes are more likely to be used in policy making decisions, and can be measured through the use of medical record data, participant self-report, and influenza testing kits or swabs to be sent to a laboratory for testing. Indeed, the COVID-19 pandemic has demonstrated that such methodologies are feasible and acceptable to the general public, with most people in the UK having completed a rapid at-home test, or returned a swab sample via post for laboratory testing, indicated by over 277 million COVID-19 tests having been carried out to date (Public Health England, 2021c).

An additional avenue for future research previously identified is the potential benefit of targeting the intervention so that participants are those who are likely to experience the largest increases in positive mood from pre- to post-intervention. Both the qualitative data and quantitative analyses further suggested that those who have the lowest levels of positive mood at baseline had the largest increases in mood from pre- to post-intervention. It was therefore suggested in Chapter 8 (section 7.3.1.2), that focusing on individuals with the greatest potential for mood increase, i.e. those with low positive mood at baseline, may result in a bigger effect of the intervention. The potential clinical benefit of focusing on this population is also large, given that vaccines may be even less effective in those with low mood and/or depression (e.g. Irwin et al., 2013).

Additionally, whilst several plausible explanations have been provided regarding the null findings for the effect of the interventions on antibody response to vaccination, it is worth considering that these results may be due

to positive affect interventions not working. Given the evidence for other psychological factors, such as stress and negative affect, these factors, either alone or in combination, may warrant further exploration. While the observational study undertaken as part of this programme of work indicated that positive affect was the most predictive factor of those measured, it is only one study with several limitations, as previously outlined. Other studies have indeed found evidence for other factors impacting vaccine response, including psychological factors such as stress and negative affect (as discussed in Chapters 2 and 3), as well as behavioural factors such as physical activity (Pascoe et al., 2014), sleep (Lange, Perras, Fehm, & Born, 2003), nutrition (Calder, 2013), and social support (Moynihan et al., 2004). Therefore, future work might want to also consider factors beyond just positive affect.

Finally, as discussed in Chapter 2 of this thesis, as well as valence, affect can also differ according to level of arousal, or activation. The positive mood interventions described and tested as part of the For-ME trial were high arousal interventions, designed to increase high arousal positive moods. Results of the trial indeed show that both interventions were able to significantly increase arousal, as indicated by both the affective slider arousal and D-VAMS sleepy-alert subscales. However, the qualitative findings in Chapter 8 suggest that some participants value low arousal positive affect, and would have liked to have seen this as part of the intervention. Whilst most of the evidence regarding positive affect focuses on high arousal interventions, there is some research suggesting no difference between high and low arousal in terms of positive affect in terms of their effect on immune parameters. This thesis is unable to address whether high or low arousal interventions are more effective regarding their effect on both mood and

immune outcomes. However, given that they may be preferred by some participants, and that they may be equally effective as suggested by the evidence, future research may want to consider the inclusion of such low arousal content.

9.8 Chapter summary

The first section of this chapter aimed to provide a brief summary of findings for the three studies comprising this thesis, with the latter section providing a discussion of their clinical, theoretical and methodological implications, as well as reflections on the challenges faced carrying out the research and ideas for future research. As part of this discussion, the use of choice in clinical practice was advocated for, and, given the potential limitations of the presented research, clinicians were encouraged to consider the role of mood pre-vaccination for both older adults receiving influenza, and more broadly. The results of the For-ME study were discussed in relation to current models of positive affect and immune function, before discussing the methodological implications, such as the method of assessing positive mood. Reflections included the challenges of recruitment and the treatment of the usual care arm. Finally, a number of avenues for future research were discussed, including a series of mechanistic studies to better understand how the intervention may work, thus resulting in a potentially more effective intervention, as well as a definitive trial sufficiently powered to detect changes in immunological outcomes, as well as the specific outcomes and populations that may be most helpful in such a trial.

10 References

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11 Appendices

Appendix A. Chapter 4: Search terms

Generic search terms1. choice*.ti,ab.

2. choose*.ti,ab.

3. chose*.ti,ab.

4. tailor*.ti,ab.

5. personali#e*.ti,ab.

6. individuali#e*.ti,ab

7. customi*.ti,ab.

8. pick*.ti,ab.

9. prefer*.ti,ab.

10. subject directed.ti,ab.

11. subject selected.ti,ab.

12. participant directed.ti,ab.

13. participant selected.ti,ab.

14. patient directed.ti,ab.

15. patient selected.ti,ab.

16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. random*.ti,ab.

18. clinical trial.ti,ab.

19. controlled clinical trial.ti,ab.

20. randomi*ed controlled trial.ti,ab.

21. trial.ti,ab.

22. 17 or 18 or 19 or 20 or 21

23. adhere*.ti,ab.

24. compliance.ti,ab.

25. comply.ti,ab.

26. screen*.ti,ab.

27. alcohol.ti,ab.

28. exercis*.ti,ab.

29. physical activity.ti,ab.

30. psycholog*.ti,ab.

31. behavi#r*.ti,ab.

32. psychobehavi#ral.ti,ab.

33. smoking.ti,ab.

34. diet.ti,ab.

35. weight loss.ti,ab.

36. walking.ti,ab.

37. step*.ti,ab.

38. depress*.ti,ab.

39. anxi*.ti,ab.

40. stress.ti,ab.

41. mood.ti,ab.

42. positive affect.ti,ab.

43. negative affect.ti,ab.

44. agitat*.ti,ab.

45. cognitive function*.ti,ab.

46. health*.ti,ab.

47. disease.ti,ab.

48. pain.ti,ab.

49. fall*.ti,ab.

50. symptom*.ti,ab.

51. diabetes.ti,ab.

52. asthma.ti,ab.

53. arthritis.ti,ab.

54. stroke.ti,ab.

55. fatigue.ti,ab.

56. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55

57. intervention.ti,ab.

58. group.ti,ab. à group*

59. arm.ti,ab.

60. condition.ti,ab.

61. manipulat*.ti,ab.

62. 57 or 58 or 59 or 60 or 61

63. 16 and 22 and 56 and 62

64. limit 63 to human

Search strategy for Medline RCT search terms

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. clinical trials as topic.sh.

6. randomly.ab.

7. trial.ti.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. exp animals/ not humans.sh.

10. 8 not 9

Search strategy for Embase RCT search terms

1. random*:ab,ti

2. placebo*:de,ab,ti

3. (double NEXT/1 blind*):ab,ti

4. 1 or 2 or 3

Search strategy for PsychInfo RCT search terms

1. double-blind

2. random* assigned

3. control

4. 1 or 2 or 3

Appendix B. Chapter 4: Example data extraction sheet

Study details

ID	Reference	Authors	Year	Funding	Country	Number of participants	Subsidary papers
2		Bartley, Faasse, Horne, Petrie	2016	Pharmac New Zealand (the New Zealand Government's Pharmaceutical Management Agency)	New Zealand	61	

Population details

ID	Authors	Ethnicity	Age	Gender	Inclusion criteria	Exclusion criteria
2	Bartley, Faasse, Horne, Petrie	European 48.3%, Asian 31.7%	Mean 21.1 years (SD = 2.78)	41 females, 20 males	University students	Currently taking any medication that could interact with beta-blocker medication (beta-blocker, calcium channel blockers, digoxin) or had any medical conditions in which beta-blocker medication use is contraindicated (asthma, diabetes, bronchospasms, low heart rate, blood pressure below 100/60 mmHg, pregnancy, or known allergies to betablockers or inert binding agents)

Intervention details

ID	Authors	Description of choice intervention	Number of options in choice intervention	Type of choice in choice intervention	Length of choice intervention	Description of no-choice intervention	Length of no-choice intervention	Number of participants in choice intervention	Number of participants in no-choice intervention
2	Bartley, Faasse, Horne, Petrie	Participants could choose between two beta-blockers	2	Same classification	One off	Participants were randomly assigned to one of the two beta-blockers	One off	29	32

Outcome details

ID	Authors	Outcome 1	Outcome 2	Outcome 3
2	Bartley, Faasse, Horne, Petrie	**Outcome 1** Protocol outcome: Mood Outcome as in paper: Anxiety Scale/measure/definition: Short-form State-Trait Anxiety Inventory, 6-24, high score = poor outcome (high anxiety) Time point: Unclear Result: - Choice group (n=29): Mean 8.66, SE 0.26 (95 % CI [8.13, 9.18]) - No-choice group (n=31): Mean 8.68, SE 0.25 (95 % CI [8.18, 9.19])	N/a	N/a

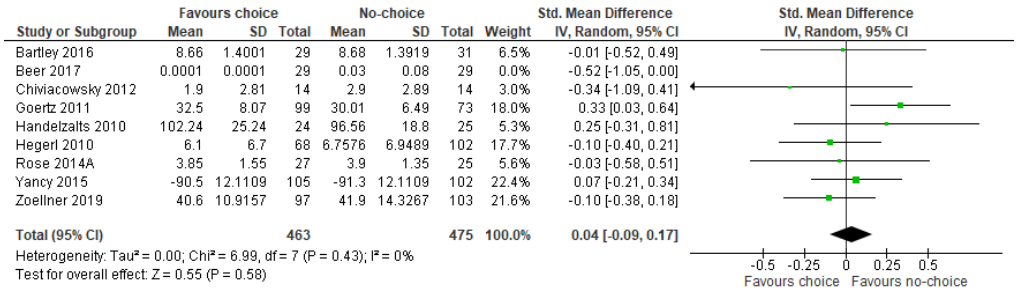
Appendix C. Chapter 4: Details of studies that could not be meta-analysed

Table C.1: Details of studies that could not be meta-analysed

Study	Outcome	Result in Choice Group	Result in No-Choice Group	Comments
Hack et al. (2003)	Mood outcomes Satisfaction	- - -	- - -	Not reported in terms of choice vs no-choice
Hack et al. (2007)	Mood outcomes Satisfaction	- - -	- - -	Not reported in terms of choice vs no-choice
Jolly et al. (2011)	Adherence to intervention	-	-	Data not reported for all no-choice subgroups
Myers and Branthwaite (1992)	Drop-out	Overall rate only reported: 26.97%		Not reported in terms of choice vs no-choice
Noël et al. (1998)	Drop-out	Overall rate only: 166/596		Not reported in terms of choice vs no-choice
Pearson et al. (2005)	Anxiety	-	-	Not reported in terms of choice vs no-choice
Rokke et al. (1999)	Depression	'No significant differences' p > .10		Means and SD not reported
ROSE ET AL. (2012)	Anxiety	2.98 (1.56)	4.56 (2.03)	Number of participants in each group not reported
Rotton and Shats (1996)	Distress	-	-	Not reported in terms of choice vs no-choice
Scott et al. (2004)	Satisfaction	-	-	Not reported in terms of choice vs no-choice
van Weert et al. (2005)	Emotional problems Satisfaction	- -	- -	Not reported in terms of choice vs no-choice
Wallston et al. (1991)	Anxiety	-	-	Only reported in terms of desire for control in the choice and no-choice groups; Means and SD not reported

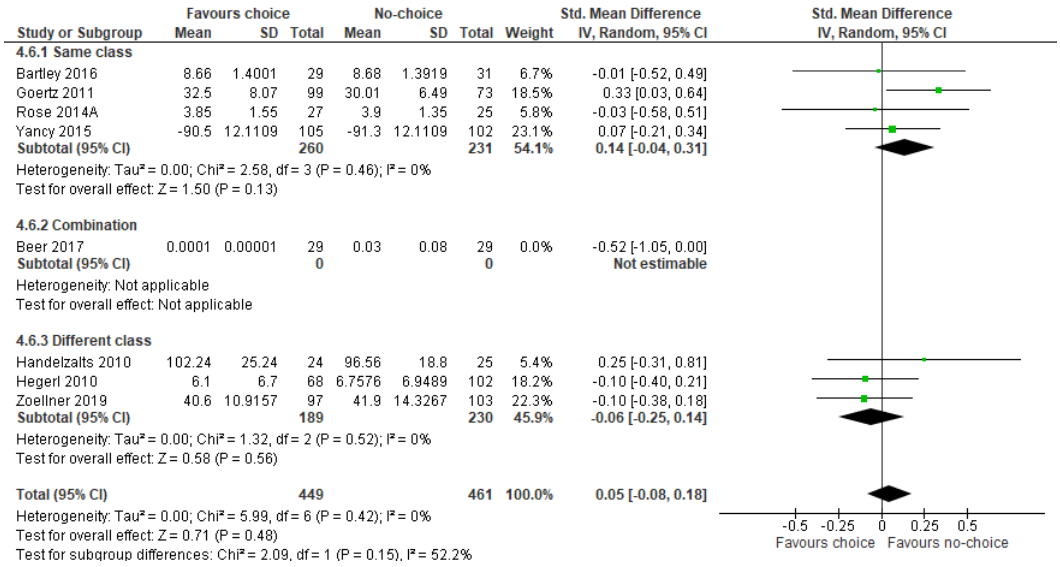
Appendix D. Chapter 4: Sensitivity analyses (Removing Beer et al., 2017)

Figure D.1 Total negative mood



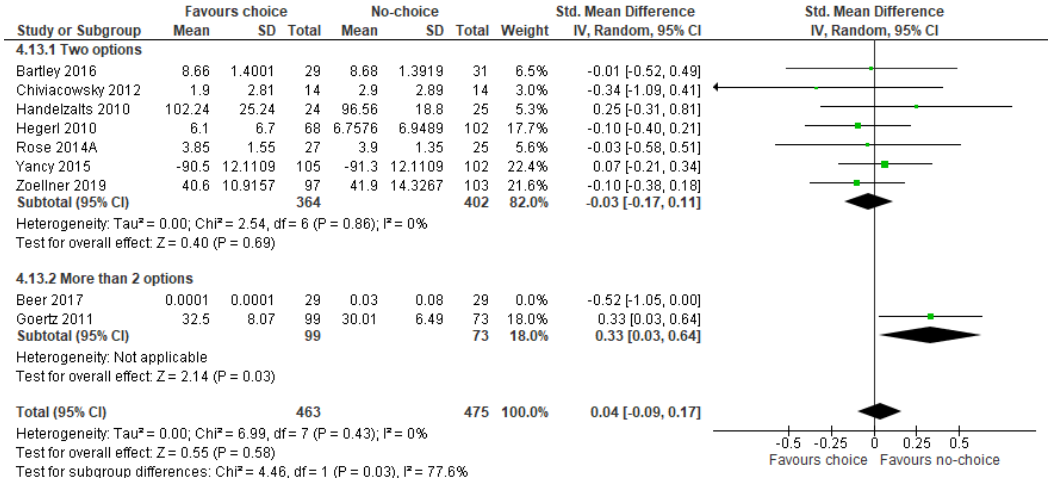
Note: Bartley 2016: short-form State-Trait Anxiety Inventory; Beer 2017: Profile of Mood States – Adolescent Inventory; Chiviacowsky 2012: non-validated questionnaire; Goertz 2011: State-Trait Anxiety Inventory – State; Handelzalts 2010: Sarason's Test Anxiety; Hegerl 2010: Hamilton Depression Rating Scale; Rose 2014A: aggregated likert scales for irritated, uncomfortable and unpleasant; Veitch 2000: non-validated questionnaire – pleasure subscale; Yancy 2015: Impact of Weight on Quality of Life-Lite questionnaire – distress subscale; Zoellner 2019: Spielberger State-Trait Anxiety Inventory

Figure D.2: Negative mood according to the type of choice



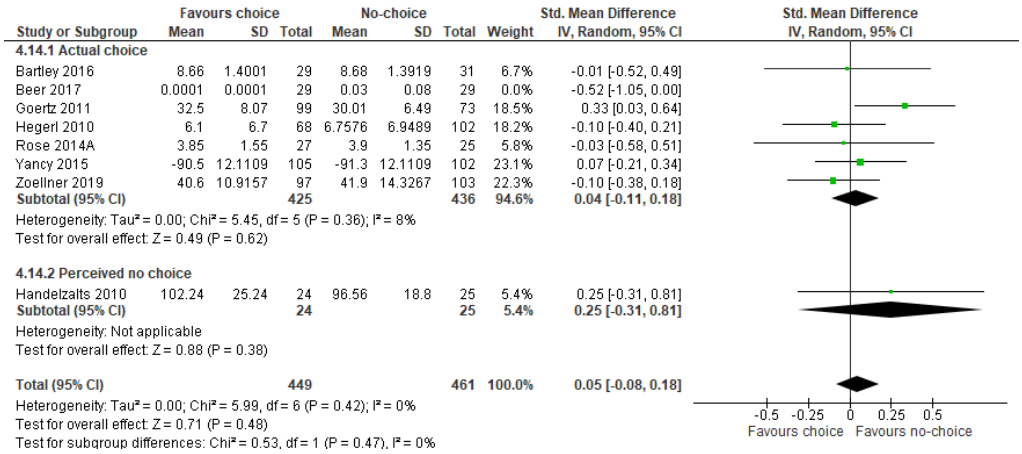
Note: Bartley 2016: short-form State-Trait Anxiety Inventory; Beer 2017: Profile of Mood States – Adolescent Inventory; Chiviacowsky 2012: non-validated questionnaire; Goertz 2011: State-Trait Anxiety Inventory – State; Handelzalts 2010: Sarason's Test Anxiety; Hegerl 2010: Hamilton Depression Rating Scale; Rose 2014A: aggregated likert scales for irritated, uncomfortable and unpleasant; Veitch 2000: non-validated questionnaire – pleasure subscale; Yancy 2015: Impact of Weight on Quality of Life-Lite questionnaire – distress subscale; Zoellner 2019: Spielberger State-Trait Anxiety Inventory

Figure D.3: Negative mood according to the number of choice options



Note: Bartley 2016: short-form State-Trait Anxiety Inventory; Beer 2017: Profile of Mood States – Adolescent Inventory; Chiviacowsky 2012: non-validated questionnaire; Goertz 2011: State-Trait Anxiety Inventory – State; Handelzalts 2010: Sarason's Test Anxiety; Hegerl 2010: Hamilton Depression Rating Scale; Rose 2014A: aggregated likert scales for irritated, uncomfortable and unpleasant; Veitch 2000: non-validated questionnaire – pleasure subscale; Yancy 2015: Impact of Weight on Quality of Life-Lite questionnaire – distress subscale; Zoellner 2019: Spielberger State-Trait Anxiety Inventory

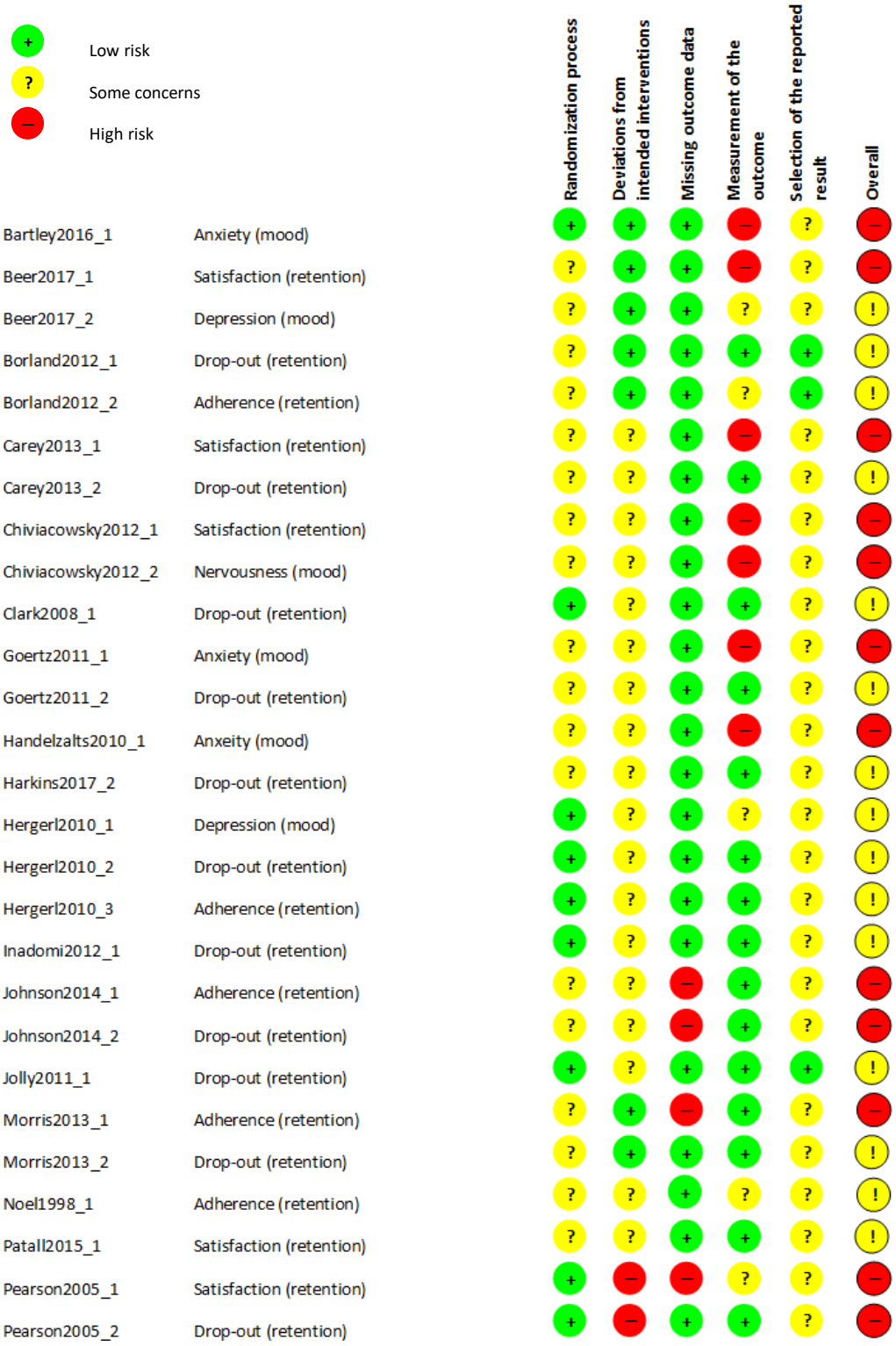
Figure D.4: Negative mood according actual choice or perceived no-choice



Note: Bartley 2016: short-form State-Trait Anxiety Inventory; Beer 2017: Profile of Mood States – Adolescent Inventory; Chiviacowsky 2012: non-validated questionnaire; Goertz 2011: State-Trait Anxiety Inventory – State; Handelzalts 2010: Sarason's Test Anxiety; Hegerl 2010: Hamilton Depression Rating Scale; Rose 2014A: aggregated likert scales for irritated, uncomfortable and unpleasant; Veitch 2000: non-validated questionnaire – pleasure subscale; Yancy 2015: Impact of Weight on Quality of Life-Lite questionnaire – distress subscale; Zoellner 2019: Spielberger State-Trait Anxiety Inventory

Appendix E. Chapter 4: Risk of bias ratings

Figure E.1: Risk of bias ratings for meta-analysed outcomes



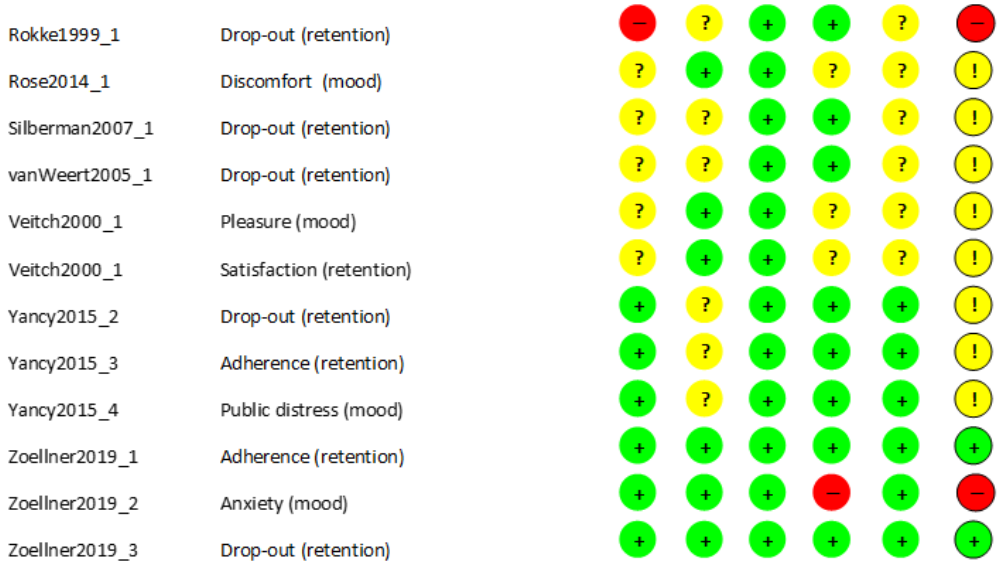
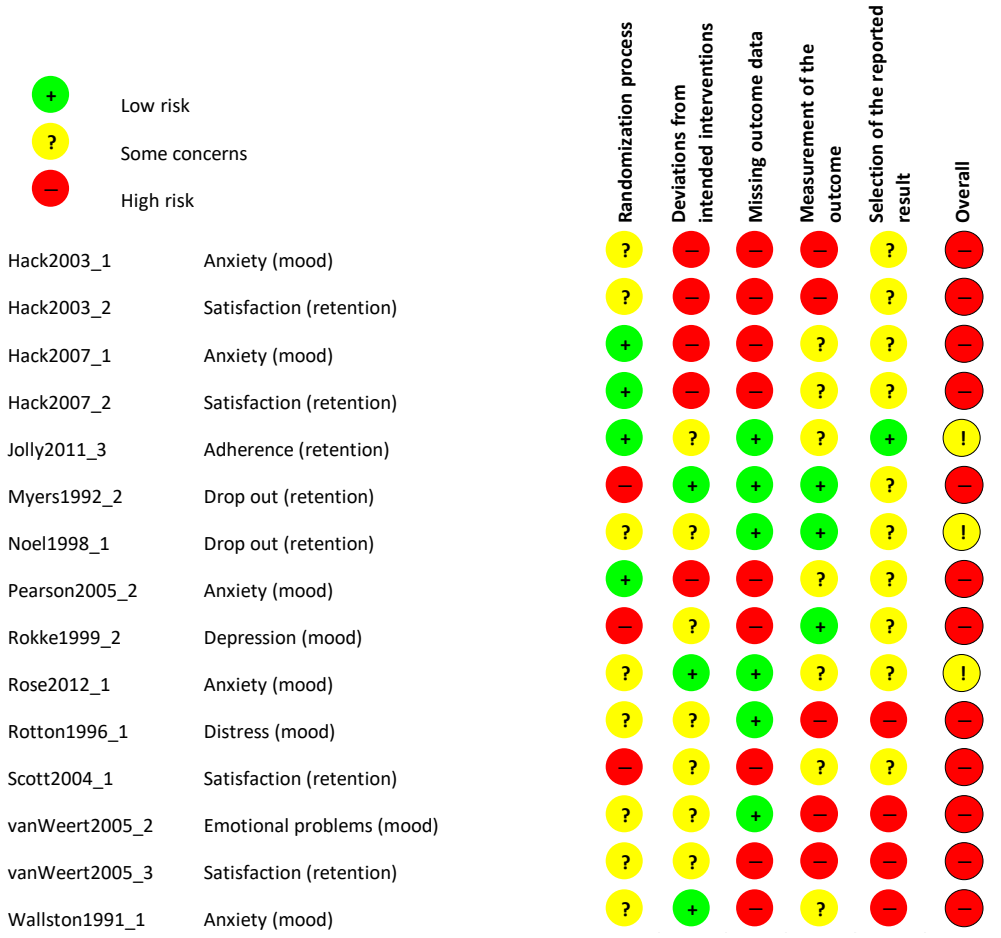


Figure E.2: Risk of bias ratings for outcomes that could not be meta-analysed



Appendix F. Chapter 5: ELISA protocol

Sample preparation

1. Thaw 167 sera samples and the 24 common samples
2. Pipette 200ul of each sera sample into the 96-well plate
3. Cover 96-well plate and return to freezer

Antigen coating

1. Coat 384-well plate with antigens
    a. Thaw antigens
    b. Dilute antigens to 0.05%. For one day a total of 8ml is required
        i. 40ul antigen + 7.96ml carbonate-bicarbonate
        ii. Repeat for each antigen
        iii. Multiply as necessary for number of plates being coated
    c. Add 20ul to each well of a 384-well plate (one 384-well plate per antigen)
2. Centrifuge 384-well plates for 3 minutes
3. Cover 384-well plates and store in refrigerator at 4˚C for at least 12 hours overnight

Blocking

1. Prepare blocking buffer
    a. For 500mls use 50ml BSA 30% and 450mls PBS
2. Aspirate and wash the 384-well plates three times using plate washing robot
    a. Use 0.05% Tween-20 in PBS as the washing agent

b. Leave plates in the PBS tween wash until ready to add blocking buffer to prevent plates from drying

3. Add blocking buffer
    a. Add 40uls per well of the blocking buffer to each plate
4. Centrifuge for 3 minutes
5. Cover and return to in refrigerator at 4˚C until needed for analysis

Analysis

1. Sera sample dilution
    a. Thaw neat sera samples and control samples in 96-well plates
    b. Serial dilute sera samples in 96-well plates to result in a 1:2000 sera dilution using BSA diluted to 3% in PBS.
    c. Aspirate and wash the 384-well plates three times using plate washing robot
        i. Use PBS tween as the washing agent
        ii. Stagger plate washing to minimise the amount of time plate is dry
2. Sera samples
    a. Add 20ul per well of the 1:2000 dilution to the 384-well plates
    b. Centrifuge 384-well plates for 3 minutes
    c. Incubate for 1 hour at room temperature using plate shaker
3. Biotinylated antihuman IgG
    a. Thaw prepared antihuman IgG stored in freezer at a 1:100 dilution
    b. Add 100ul thawed anti-human IgG to 30ml PBS for 1:30000 dilution

c. After the 1 hour incubation aspirate and wash the 384-well plates three times using plate washing robot
    i. Use PBS tween as the washing agent
    ii. Stagger plate washing to minimise the amount of time plate is dry
d. Add 20ul per well of the 1:30000 antihuman IgG to each 384-well plate
e. Centrifuge for 3 minutes
f. Incubate for 1 hour at room temperature using plate shaker

4. TMB
    a. Measure 25mls of TMB
    b. Store at room temperature somewhere dark until ready for use
    c. After the 1 hour incubation, aspirate and wash the 384-well plates three times using plate washing robot
        i. Use PBS tween as the washing agent
        ii. Stagger plate washing to minimise the amount of time plate is dry
    d. Add 20ul of TMB to each well of each 384-well plate
    e. Centrifuge each plate as soon as the TMB has been added for 3 minutes
5. Stopping solution
    a. Add 20µl per well of the stopping solution (1-2N sulfuric acid)
    b. Centrifuge each plate
6. Read optical densities of each plate using the optical scanner

Appendix G. Chapter 6: Analysis of post-intervention scores only in the ITT population

Mood related analyses

Combined intervention (standard and choice groups) versus usual care

Table G.1: Mann-Whitney U test to assess for differences between the combined intervention group and usual care in terms of post-intervention affective slider: pleasure scores

	U	*Z*	*p*	r
Affective slider: pleasure	24684.50	-3.19	.001	-.128

Note: Mann-Whitney U test was performed due to violations of the assumptions of normal distribution and homogeneity of variance

Table G.2: Mann-Whitney U test to assess for differences between the combined intervention group and usual care in terms of post-intervention secondary mood-related scores

	U	*Z*	*p*	r
Affective slider: arousal	28151.00	-1.43	.154	-.057
D-VAMS: happy-sad	22674.00	-4.13	< .001	-.167
D-VAMS: sleepy-alert	24935.50	-2.58	.010	-.104
SPANE: positive	26058.50	-3.29	.001	-.130
SPANE: negative	24281.00	-4.46	< .001	-.178

Note: Mann-Whitney U test was performed due to violations of the assumptions of normal distribution (affective slider arousal; D-VAMS happy-sad; D-VAMS sleepy-alert; SPANE positive; SPANE negative) and homogeneity of variance (affective slider arousal; D-VAMS happy-sad; D-VAMS sleepy-alert; SPANE negative)

Standard intervention versus choice intervention versus usual care

Table G.3: Kruskal Wallis test to assess for differences between the three study groups in terms of post-intervention affective slider pleasure scores

	df	*H*	*p*	*U*	*p*	*r*
Affective slider: pleasure	2	11.30	.004			
- 0 versus 1				12549.00	.010	-.134
- 0 versus 2				12023.50	.001	-.172
- 1 versus 2				29724.50	.342	-.042

Note: Kruskal Wallis test was performed due to violations of the assumptions of normal distribution and homogeneity of variance.
Note: Post-hoc tests are Mann-Whitney U tests
Note: 0 = usual care, 1 = standard intervention, 2 = choice-based intervention

Table G.4: Kruskal Wallis test to assess for differences between the three study groups in terms of post-intervention affective slider pleasure scores

	df	*H*	*p*	*U*	*p*	*r*
Affective slider: arousal	2	2.53	.282			
0 versus 1				14049.00	.287	-.055
0 versus 2				13971.50	.120	-.080
1 versus 2				30237.00	.481	-.031
D-VAMS: happy-sad	2	17.47	< .001			
0 versus 1				11412.00	< .001	-.188
0 versus 2				11286.50	< .001	-.206
1 versus 2				29744.50	.578	-.025
D-VAMS: sleepy-alert	2	6.61	= .014			
0 versus 1				12926.00	.070	-.095
0 versus 2				12113.50	.005	-.148
1 versus 2				28239.00	.132	-.067
SPANE: positive	2	13.26	= .001			
0 versus 1				13670.50	.018	-.121
0 versus 2				12388.00	< .001	-.186
1 versus 2				30419.00	.120	-.069
SPANE: negative	2	19.10	< .001			
0 versus 1				12407.50	< .001	-.189
0 versus 2				12111.50	< .001	-.210
1 versus 2				31202.00	.577	-.025

Note: Kruskal Wallis test was performed due to violations of the assumptions of normal distribution (affective slider arousal; D-VAMS happy-sad; D-VAMS sleepy-alert; SPANE positive; SPANE negative) and homogeneity of variance (affective slider arousal; D-VAMS happy-sad; D-VAMS sleepy-alert; SPANE negative).
Note: Post-hoc tests are Mann-Whitney U tests
Note: 0 = usual care, 1 = standard intervention, 2 = choice-based intervention

Antibody-related analyses

Combined intervention (standard and choice groups) versus usual care

Table G.5: Independent sample t-test to assess for differences between the combined intervention group and usual care in terms of post-vaccination antibody levels

	df	***t***	***p***	**r**
A/Kansas (H3N2)	585	-0.06	.951	.003
B/Maryland (B)	582	1.05	.292	.044
A/Brisbane (H1N1)	583	0.66	.511	.027

Standard intervention versus choice intervention versus usual care

Table G.6: One-way independent ANOVA to assess for differences between the three study groups in terms of post-vaccination A/Kansas and A/Brisbane antibody levels

	df	***F***	***p***	**ω^2**
A/Kansas (H3N2)	2, 584	0.95	.388	.000
A/Brisbane (H1N1)	2, 582	0.68	.508	-.001

Table G.7: Kruskal Wallis test to assess for differences between the three study groups in terms of post-vaccination B/Maryland antibody levels

	df	***H***	***p***
B/Maryland (B)	2	2.764	.251

Note: Kruskal Wallis test was performed due to violations of the assumption of homogeneity of variance

Appendix H. Chapter 6: Sensitivity analyses

Research question 2.1: Hypothesis 1

Sensitivity analyses removing parametric assumptions

Table H.1: Quade's ranked ANCOVA to compare the three intervention groups in terms of the primary outcome and secondary mood-related outcomes at post-intervention with pre-intervention values included as covariates

	df	***F***	***p***	**Partial η^2**
Affective slider: pleasure	613	10.92	< .001	.034
Affective slider: arousal	612	3.29	.038	.011
D-VAMS: happy-sad	606	20.95	< .001	.065
D-VAMS: sleepy-alert	602	10.02	< .001	.032
SPANE: positive	623	12.84	< .001	.040
SPANE: negative	609	6.84	.001	.022

Note: Quade's ranked ANCOVA was performed due to violations of the assumption of homogeneity of variance for the SPANE: negative outcome, and homogeneity of regression slopes for all other outcomes.

Research question 3.1: Hypothesis 1

Sensitivity analyses with baseline corrected scores

Table H.2: ANCOVA to compare the combined intervention group and the usual care group in terms of post-vaccination antibody levels for the three vaccine strains using baseline corrected values

	df	***F***	***p***	ω^2
A/Kansas	583	0.53	.469	- .001
B/Maryland (B)	582	0.05	.832	- .002
A/Brisbane	583	0.16	.689	- .001

Research question 3.1: Hypothesis 2

Sensitivity analyses removing parametric assumptions

Table H.3: Quade's ranked ANCOVA comparing post-intervention antibody levels between participants who received the choice intervention, standard fixed contentment intervention, or usual care

	df	***F***	***p***	**Partial η^2**
B/Maryland (B)	581	.55	.580	.002

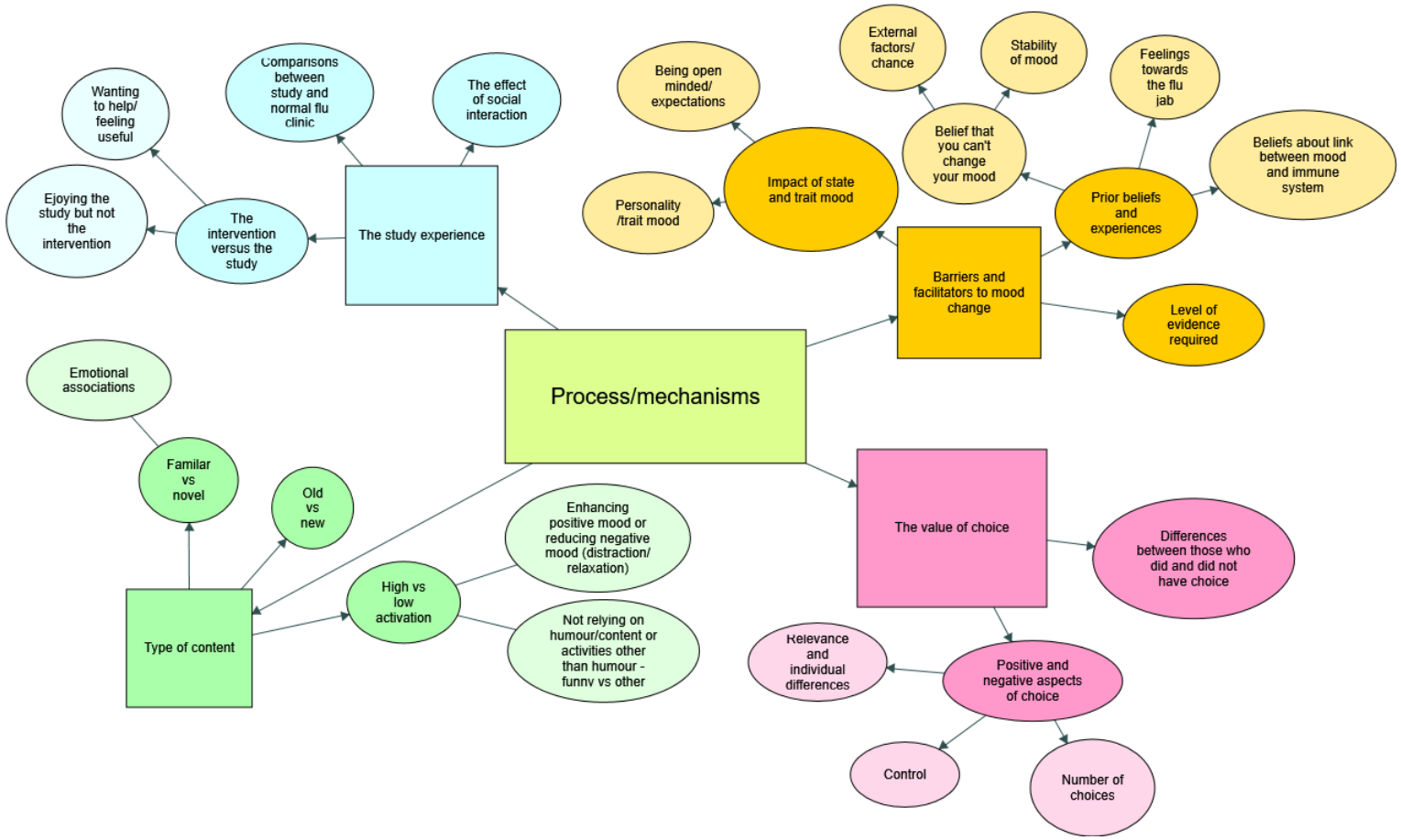
Note: Quade's ranked ANCOVA was performed due to violations of the assumption of homogeneity of regression slopes for the B/Maryland antigen strain.

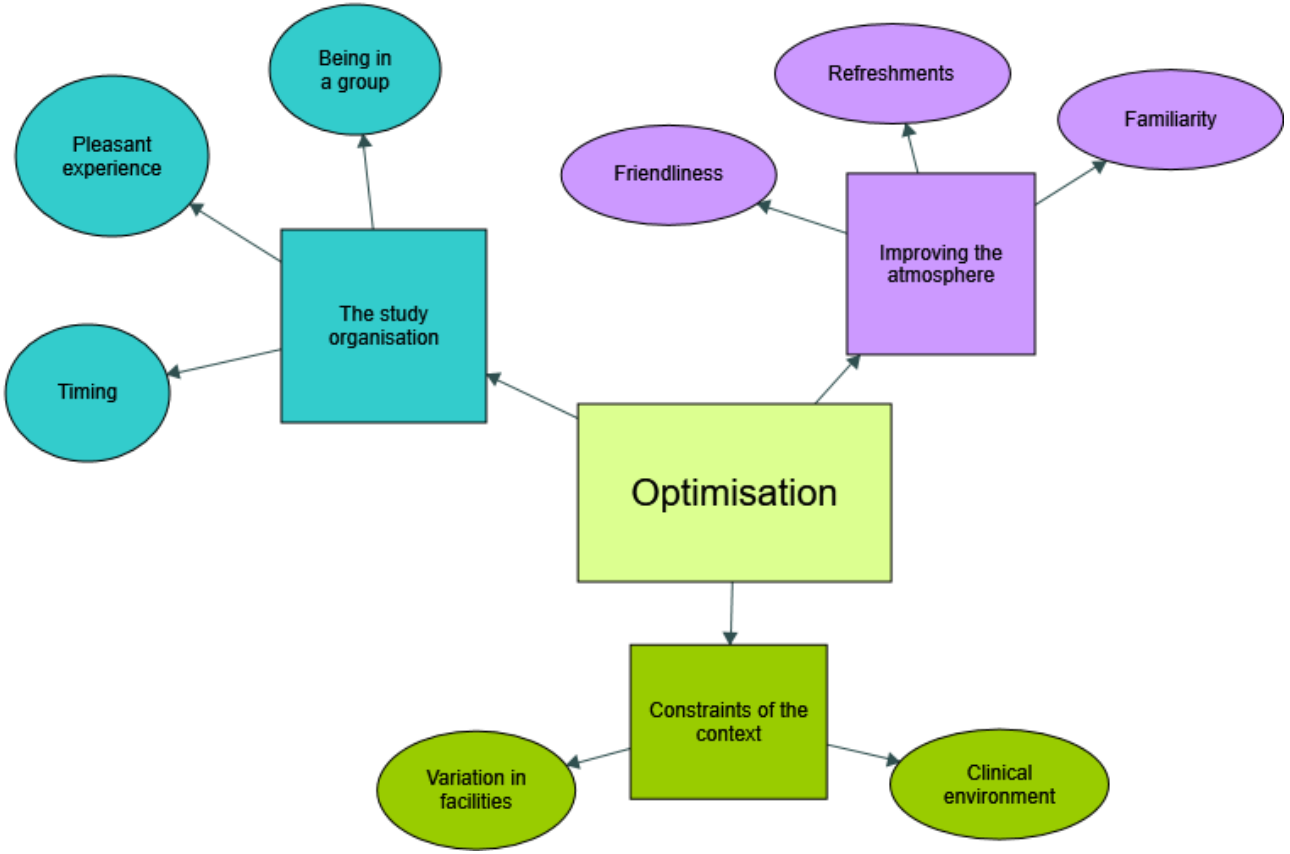
Sensitivity analyses with baseline corrected scores

Table H.4: One-way ANCOVAs to compare the three groups in terms of the post-vaccination antibody levels for the three vaccine strains using baseline corrected values

	df	***F***	***p***	ω^2
A/Kansas	583	0.78	.460	- .001
B/Maryland	581	0.19	.827	- .003
A/Brisbane	582	0.70	.496	- .001

Appendix I. Chapter 8: Thematic map




Being in a group
Pleasant experience
Refreshments
Familiarity
Friendliness
Improving the atmosphere
The study organisation
Timing
Optimisation
Constraints of the context
Variation in facilities
Clinical environment