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Epidemiology Network Analysis

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Preface

Social influence has been a notion nesting in human brains since we started living in a community. In the Poetic Edda, the poems of Fáfnismál [1] [2] and Völuspá [3] describe the existence of beings known as the “Nornir”, who are in charge of weaving the threads of destiny for gods and humans alike. Völuspá describes the Nornir as three individuals: Urðr (“Fate”), Verðandi (“What Is To Come”), and Skuld (“What Needs To Occur”). In Germanic folklore, fate is not fixed nor unique. Because of the influence of others, and because of our own past actions, humans do not have complete freedom to do what they want, but we are not enslaved by divine determinism either. The Nornir are constantly knitting the tapestry of life, in which each person’s string is tugging with those of others, always changing and defining who we are or will be.

A thousand years later, Jean Jacques Rousseau argues that we surrender our freedom to the "community". Rousseau synthesized the transition from natural freedom to civil liberty with the phrase: "*Freedom consists not so much in doing one's will as in not being subjected to that of others; it still consists in not submitting the will of others to ours*" [4]. Rousseau argued that one must surrender his freedom and act in the best interest of the "general will" because by definition the general will can never be wrong. This "general will" has been used as justification for preserving liberty and to build the foundations for 20th-century totalitarianism enforcing oppression. In contrast, John Locke argued that there are rights undeniable to each individual, and no government, not even the general will, has the right to take them away.

This begs the question, if other people always influence us and we are vulnerable to others' ideas, is freedom an illusion? In my thesis, I argue that your health is not different and will never be alone. Your social network has been estimated to weigh between 15% to 40% [5] of the relative contributions from health determinants (such as genetics, environment, or medical care) to health outcomes. You are forced to be part of a community and you need to understand the trade-off of your options. People give you the risk of being infected by pathogens, but isolation makes you more likely to have

alcohol addiction or suffer from depression. Friends will influence you to skip diets and drinks at the bar, advertisers will constantly push you to consume junk food. Do you eat what you want or do you eat what is enforced upon you? Do you choose your health or is it imposed by others?

You are locked in the tapestry with other people and they are always influencing your fate, but you are still in charge of it. Being part of a group doesn't excuse you from being responsible for your actions. Being aware of that influence allows you to act with freedom and not necessarily by obeying the will of others. I invite you to read this work and how we measure such influences and their consequences, how to recognize them, and how to avoid them, in the hope that you use this knowledge to preserve the elemental health rights of individuals.

This thesis is the product of my work at the Department of Computer Science, UiT The Arctic University of Norway, Tromsø, to obtain the Philosophiae Doctor of Science.

Rafael Adolfo Nozal Cañadas January 10, 2024

Abstract

Research questions: The primary objective of this doctoral dissertation is an explorative investigation into the social network dynamics within eight high schools, located in Tromsø and Balsfjord (North Norway), and the extent to which these dynamics contribute to the overall health and well-being of the students, such as in the context of infectious disease spread and the transmission of negative or positive health effects, and also in comparison with non-social host factors such as sports or recreational drug frequencies. Secondarily, we aim to develop new analytical methods and provide a framework for enabling agnostic evaluation of social networks in epidemiological studies and faster iterations of developing scripts for general statistical research.

Methodology: Using the Fit Futures gathered data on friendship, we used simulations, homophily, X^2 tables, logistic regression, and random forests as the main methods to analyze social influence in our topics of interest. We applied classical database normalization and data cleaning to the original data and developed scripts for automatic analysis in R and Python exporting results directly in plain text, Latex, and HTML.

Results: We found that the social network influences significantly the spread of *Staphylococcus aureus* (*S. aureus*). Students close in the network tend to have similar inflammatory biomarkers, 25-hydroxyvitamin D (25(OH)D), and Body mass index (BMI) levels. Some high schools tend to consume similar levels of over-the-counter medicines and tend to share the same brand of prescribed medicines. There is also a bias on recreational drug usage by high school.

Conclusions: Social influence is shown to be significant in every analysis. These findings emphasize the importance of considering social network dynamics in understanding and addressing health and well-being issues among students. Further research and interventions targeting social network influences can contribute to developing more effective health strategies.

Originality: Use of non-parametric simulation and machine learning methods to estimate social influence. We are measuring social influence on 25(OH)D, in an inflammatory proteomic assay.

Significance: Social influence, whether from virtual friends or physical ones, is a growing area of interest in many fields. In Epidemiology in particular we saw a boost in popularity after the Sars-Cov-2 pandemic.

Keywords: Social Networks, *S. aureus*, statistics, epidemiology, vitamin D, obesity, inflammation, random forests, prescriptions, drugs.

Acknowledgements

A fair listing of all the positive qualities and contributions of everyone connected to this thesis would render another 200 pages, and would still be the short version of it. Instead, I hope that the people named here would forgive me for describing only one or two of the many good characteristics that helped in this PhD journey.

First, I want to express my gratitude to Befolkningsundersøkelser i nord (BiN) and the UiT The Arctic University of Norway for providing financial support, and The Regional Committee of Medical and Health Research Ethics (REK) and the Norwegian Data Protection Authority for approval of the data collection (reference: 2018/1975/REK Nord).

I would like to express my sincere gratitude to my main supervisor Lars-Ailo Bongo for his invaluable contributions to this project. His writing feedback has been incredibly thorough and detailed, providing me with the guidance and support I needed to refine my work and take it to the next level. In addition, his high level of expertise and knowledge in many fields has been instrumental in shaping the direction and scope of this project. His insights and recommendations have been invaluable, and I feel fortunate to have had the opportunity to work with someone of such exceptional talent and dedication.

Co-supervisors Anne-Sofie Furberg and Anne Merethe Hanssen have provided valuable insights and expertise in the areas of general medicine and microbiology, which have helped to shape this project, and been a source of moral support throughout this project, providing encouragement and motivation. They have also introduced me to other individuals, listed below, who have later made significant contributions to this project.

Christopher Nilsen for his invaluable contributions to this doctoral thesis. Christopher played a pivotal role in the conceptualization of Fit Futures. In particular, he also insisted on the inclusion of the social network data that made this PhD research possible. His foresight was critical in shaping the direction of this research and many others as he is persistently securing funding for new projects.

To my department leader Anders Andersen and his efforts to improve the department's resources thanks to which I had the means to do this PhD.

Other co-authors in this project are Dina Benedicte Berg Stensen, Mohsen Askar. I would like to express my deep appreciation to them for their invaluable contributions to the scientific articles we have worked on together. Their expertise in the fields of endocrinology and pharmacy has been essential in shaping the direction and scope of our research, and their collaboration has been instrumental in bringing these papers to fruition. Their dedication, hard work, and attention to detail have been truly inspiring, and I feel grateful to have had the opportunity to work with such talented and knowledgeable individuals.

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Other collaborators Rocío Bonillo León, Svendsen Kristian, Lars Småbrekke, Guri Grimmes. I don't have a background in medicine, but thanks to them I gained a deeper understanding of many topics, including nutrition, pharmacology, immunology, endocrinology, and physiology. For me is important to get the best mental image possible of how things work rather than crunching the numbers and hoping that someone else deals with the results.

All other group coworkers for their continuous feedback, encouragement, and dedication to showing me and others how to push the boundaries of knowledge. Also, to the cleaning crew in the UiT, for their tireless efforts, their hard work and dedication often go unnoticed, but their contributions are invaluable to the smooth operation of the university. Without their daily efforts, the university would not be able to function effectively. And finally to the personnel in charge of making food in the cafeteria. Their commitment to providing nutritious and delicious meals to the university community is greatly appreciated and kept me running many endless days in the office.

All their valuable wisdom and efforts encourage me and others to reach our full potential.

List of papers

This thesis is based on the following papers, available in the appendix section A.

Paper A: Stensen DB, Cañas RAN, Småbrekke L, Olsen K, Nielsen CS, Svendsen K, Hanssen AM, Sollid JUE, Simonsen GS, Bongo LA, Furberg AS. Social network analysis of *Staphylococcus aureus* carriage in a general youth population. International Journal of Infectious Diseases Volume 123, October 2022, Pages 200-209
<https://doi.org/10.1016/j.ijid.2022.08.018>

Paper B: The Social Sunshine of the Arctic Youth: Exploring friendship's influence on Vitamin D levels. Cañas RAN, Nielsen CS, Furberg AS, Hanssen AM, Bongo LA
<https://www.medrxiv.org/content/10.1101/2023.11.29.23299188v1.full.pdf>

Paper C: Askar M, Cañas RAN, Svendsen K. An introduction to network analysis for studies of medication use. Research in Social and Administrative Pharmacy Volume 17, Issue 12, December 2021, Pages 2054-2061 <https://doi.org/10.1016/j.sapharm.2021.06.021>

In addition, the following results are a summary of another four manuscripts that have not yet been published, which can be found in the appendix section B.

Result I: Social network influences on obesity in a general youth population

Result II: Social network influences on inflammatory response in a general youth population

Result III: Measuring social influence with random forest regression and artificial neural networks.

Result IV: Frequency consumption of medication and social network influence in a general youth population.

Abbreviations

S. aureus *Staphylococcus aureus*. iii, iv, 2, 3, 5, 9, 11, 45, 50, 60–62

1,25(OH)2D 1,25-dihydroxyvitamin D. 17

25(OH)D 25-hydroxyvitamin D. iii, iv, 16, 46

ALA alpha-linolenic acid. 14

ANNs Artificial Neural Networks. 22, 201

APR Acute phase reactants. 54

BCNF Boyce - Codd normal form. 58

BDNF Brain-derived Neurotrophic factor. 54

BiN Befolkningsundersøkelser i nord. v

BMI Body mass index. iii, 45, 54, 62

ClfA Clumping factor proteins A. 10

ClfB Clumping factor proteins B. 10

COX cyclooxygenase. 20

CRP C-reactive protein. 53

CSF1 Macrophage colony-stimulating factor 1. 54

DAMPs Internal Damage Associated Molecular Patterns. 13

DDIs drug-drug interactions. 47, 52

DHA docosahexaenoic acid. 14

DPN Drug Prescription Networks. 47

DXM Dextromethorphan. 21

EPA eicosapentaenoic acid. 14

ESR erythrocyte sedimentation rate. 54

FEST Norwegian Electronic Prescription Support System. 47

FF Fit Futures. 25, 61

FF1 Fit Futures 1. xv, 8, 45

FF2 Fit Futures 2. 25, 201

FnBPA Fibronectin binding protein A. 60

HC Hormonal contraceptives. 28

HIV Human Immunodeficiency Virus. 2, 50

ICD-10 International Statistical Classification of Diseases and Related Health Problems.
35

IDE Integrated Development Environment. 60

IFN- γ Interferon gamma. 10

IgE Immunoglobulin E. 19

IgG Immunoglobulin G. 10, 13

IgM Immunoglobulin M. 13

IL-1 Interleukin 1. 10, 15

IL-2 Interleukin 2. 10

IL-5 Interleukin 5. 15

IL-6 Interleukin 6. 15, 53

LTC4 Leukotriene C4. 15

LZRSA *Linezolid resistance in Staphylococcus aureus.* 11

M-BMs memory-based dietary assessment methods. 46, 51

MAE Mean Absolute Error. 202

MDI Mean Decrease in Impurity. 23, 48, 55, 201

MDS Multidimensional Scaling. xv, 7, 8

MEDAS 14-Item Mediterranean Diet Adherence Screener. 55

MET Metabolic Equivalent of Task. 46, 51

MHC2 major histocompatibility complex 2. 10

MRSA *Methicillin-resistant Staphylococcus aureus.* 9, 11, 50

MSCRAMM Microbial Surface Component Recognizing Adhesive Matrix Molecules.
10

NA Network Analysis. 47

NAPQI N-acetyl-p-benzoquinone imine. 19

NorPD Norwegian Prescription Database. 47

NSAIDs Nonsteroidal anti-inflammatory drug. 19, 20

OTC Over-the-counter. 5, 17–19, 21, 62

PA Physical Activity. 45, 46, 51

PAMPs Pathogen Associated Molecular Patterns. 13

PD2 Protecting D2. 15

PG prostaglandins. 20

PRRs Patter Recognition Receptors. 13

PTH Parathyroid hormone. 16

REK The Regional Committee of Medical and Health Research Ethics. v

RF Random Forests. 22, 201

RLRs RIG-I-like receptors. 13

SHAP SHapley Additive exPlanations. 23, 48, 55, 201

SNA Social Network Analysis. 1–4, 52, 62

Spa Staphylococcal protein A. 10, 30, 45

SPMs Specialized pro-resolving mediators. 13, 15, 61

SSSS Staphylococcal scalded skin syndrome. 11

TLRs Toll-like receptors. 13

TNF α Tumor Necrosis Factor α . 10, 15

TSST-1 Toxic Shock Syndrome Type-1. 10

UiT UiT: The Arctic university of Norway. 32

UNN University Hospital of North Norway. 25, 32

UVB Ultraviolet B. 46, 51

VDR Vitamin D receptor. 17

VDSP Vitamin D Standardization Program. 32

VRSA *Vancomycin-resistant Staphylococcus aureus*. 11

vWF von Willebrand factor. 12

WHO World Health Organization. 32

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Chapter 1: Introduction

1.1 Social Network Analysis in health

In recent years there has been a growing recognition of the profound impact that social relationships and networks of friends have on health outcomes (figure 1.1). This includes common and well-known topics such as the spread of obesity [10, 11], recreational drugs usage such as smoking [12, 13] alcohol [14, 15] or cannabis [16], and depression [14].

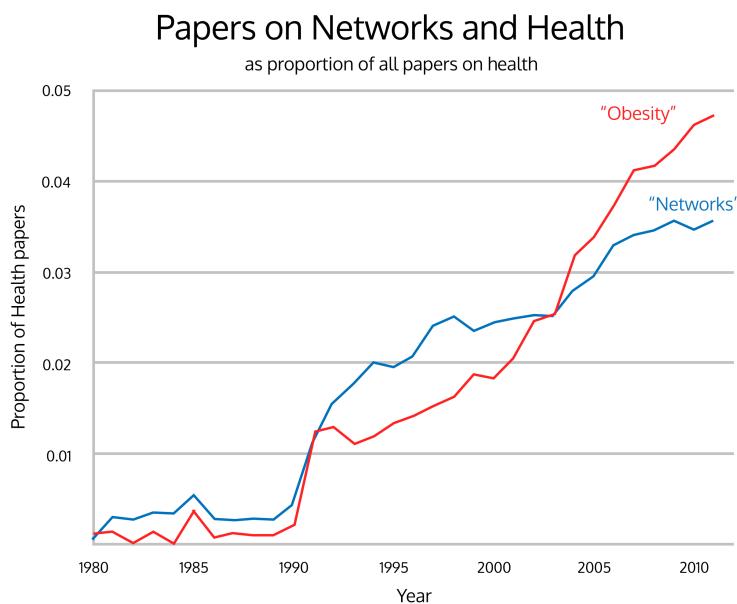


Figure 1.1: Proportion of papers published about networks on the topic of health across the years, compared with the number of papers published on obesity. Image reproduced with permissions from "International Encyclopedia of the Social and Behavioral Sciences" [6].

Social Network Analysis (SNA) is a powerful tool for understanding how social connections influence health behaviors, disease transmission, and healthcare access. This thesis leverages SNA techniques to explore the dynamic interplay between social networks and health, aiming to provide valuable insights that can inform interventions, policies, and practices for improving health outcomes.

1.2 Social network interventions

Within the realm of health research, SNA has demonstrated its versatility and applicability across a wide range of topics. It is possible to detect early outbreaks of influenza [17]. To prevent the spread of Human Immunodeficiency Virus (HIV) infections [18]. To improve the life of chronic illnesses patients as well as their families and community [19]. It has been shown that information on social networks can increase the prediction of health-related models at around 50% [20]. It has been used to design interventions and strategies to enhance communication, collaboration, and knowledge sharing among health professionals, ultimately improving the overall performance and effectiveness of the health organization [21, 22]. A systematic review of 37 studies suggests that social network interventions are associated with positive health behaviors and outcomes [23]. And of course, social network interventions have been used to better the outcome of obesity [24–27], mental health [28, 29], overcoming tobacco addiction [30, 31], transmittable diseases in humans [32–35] and in cattle such as cows, sheep, and pigs [36, 37], and recently we experienced these interventions first hand with COVID-19 [38, 39].

These few examples show that SNA has proven practical value in understanding the diffusion of diseases, as well as tracking the spread of infectious agents through clusters or interconnected social groups. It has been found to play a crucial role in improving individuals' health and preventing further deterioration of their well-being. Different authors have evaluated that social relationships influence a person's health between 15% to 40% [5], putting it ahead of the environment and even medical care. And yet it remains a vastly under-utilized and underrated technique.

1.3 Thesis impact

In this thesis, we employ SNA techniques to shed light on the complex relationships between social networks and health outcomes within a specific population. We have shown how *Staphylococcus aureus* (*S. aureus*), vitamin D, inflammation, medication usage, and obesity are influenced by social networks in a general youth population in Tromsø. We also expanded non-parametric methods for group comparisons in graphs using simulations and applied machine learning models to measure the influence of peers on obesity. Finally, we lay down the basics for a framework to obtain a more efficient analysis framework. We hope this leads to a significant contribution to public interventions and policies that ultimately lead to improved health outcomes in Norway and beyond.

Chapter 2: Aims of the thesis

The overarching objective of this research is to develop methodologies and conduct exploratory studies to evaluate the impact of social influence on a range of health-related topics. This work targets several topics and is done with the help of an interdisciplinary team of health professional researchers. In parallel, this work aims to provide a framework that enables researchers to facilitate faster analysis and produce improved visualizations.

The results of these studies must be a quantifiable measure of how much measuring or modifying the social networks could benefit the studied population. Secondarily, speculate how these results could affect the general population and the advantages and disadvantages of influencing and changing their social network.

The first step of our research is to study how infections and the immune system behave in the population. First, by measuring the spread of *S. aureus* (Paper A) and investigating the possibility that inflammatory processes may be similar across individuals or schools (Result II). The second step is to inspect the social aspect of obesity with classical methods (Result I) and using machine learning models (Result III). Lastly, we look into other variables of interest such as how friends influence vitamin D levels (Paper B) or medication usage (Result IV).

For our secondary objectives, we want to present tutorials and proof of concept on how to apply SNA techniques. For this, we choose prescriptions and drug interactions (Paper C). We also want to present a user-friendly wrapper library to abstract away the complexity and details of SNA and other statistic and machine learning models, where biases are checked automatically, fundamental analysis reports are generated with minimal intervention from the programmer, and plots or figures follow basic design rules for good visualization.

Starting with infectious diseases is a good starting point as it is the classical topic for understanding the network structure, and testing and developing new methods. It also has the advantage of updating targeted interventions in similar populations in the

future. Later on, obesity in particular is a good topic for SNA due to having a substantial impact on individual lifestyle choices, including diet, exercise, and weight management; all of which are influenced by friends. Lastly, topics such as vitamin D levels are purely explorative and we want to determine if there was a connection with the social network.

Regarding our programming objective, wrapper libraries serve as a layer of abstraction that simplifies the usage of lower-level functionality, allowing programmers to build applications more efficiently and with less effort. We also want to extend these advantages and make a high-level abstraction in the statistical context.

Chapter 3: Background

3.1 Introduction

This chapter aims to give a very short background on the interdisciplinary topics that compose this thesis. A reader of this document is assumed to have knowledge domain about these topics to minimize the thesis length. A complementary document is provided alongside this thesis and can be found at https://github.com/rafanozal/PhDThesis/blob/main/Thesis_Complementary.pdf. This document covers in more detail the mathematical principles of graphs, and the biological background for *S. aureus* (Paper A), inflammation (Result II), vitamin D (Paper B), and well as the pharmaceutical principles of Over-the-counter (OTC) medicine (Result IV), which the reader may need to understand the topics fully.

3.2 Graph theory

3.2.1 Introduction

Graph theory is a branch of mathematics that studies the properties and applications of graphs. A graph is a mathematical structure consisting of a set of vertices (also referred to as nodes) and a set of edges of these vertices [40]. It is a fascinating subject with numerous practical applications in several fields including physical network connections in computer science, optimizing logistics in transportation, or in our case measuring the influence of peers in social networks.

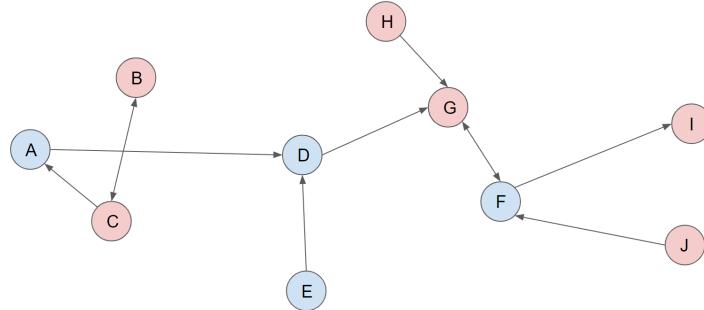


Figure 3.1: An example of a network with 10 nodes labeled from A to J. Each node has a color attribute that can be either red or blue. Nodes are connected via directed relationships. Nodes B and C, and nodes G and F have a reciprocal relationship.

Graphs provide an abstract representation of the relationships between objects, which may be used to find paths, network flow, connectivity, and more. In this context, we will talk about graphs and networks interchangeably.

A graph has the following mathematical definition:

$$G = (V, E) \quad (3.1)$$

Where G is the graph, V is the set of vertices, and E is the set of edges. In figure 3.1, we define G as $V = \{A, B, C, D, E, F, G, H, I, J\}$ and $E = \{ \{A,D\}, \{B,C\}, \{C,A\}, \{C,B\}, \{D,G\}, \{E,D\}, \{F,G\}, \{F,I\}, \{G,F\}, \{H,G\}, \{J,F\} \}$

3.2.2 Nodes

A node or vertex is the fundamental element of a network. It is usually represented as a point with lines, known as edges, coming out of it, which connect it with other nodes in the network. Each node represents one elemental object in the network, which in our case is a total of 1038 students. In different contexts, nodes can be cities, computers, or any other concept.

Mathematically, we notate all nodes as V , with each individual node in a graph with lowercase variables, such as x , y , or z . The total number of nodes is notated with $|V|$. In figure 3.1, we have 10 nodes.

Attributes

Each node may have different variables, such as sex, BMI, or any other intrinsic variable proper to the object the node is representing. Each of these variables is known as the attributes of a node. Each attribute of a node is notated with subindexes, such as $x_1, x_2, \dots, x_i, \dots, x_n$. In figure 3.1, $A_{color} = blue$

3.2.3 Edges

An edge represents a relationship between two nodes. Our network represents a relationship of undirected friendship. The assessment of friendship is formally introduced in section 4.1.1. Two nodes can have multiple edges with the same or different weights between them, or have none. In our case, all weights are equal to one as all relationships are considered of equal value. If all edges in the graph have at least one connection to every other node, then it is called a complete graph.

The mathematical definition of all edges in a graph is as follows:

$$E \subseteq \{(x, y) | (x, y) \in V^2 \wedge x \neq y\} \quad (3.2)$$

We denote the total number of edges as $|E|$. A particular edge between two nodes is simply (x, y) . In figure 3.1, we have 11 edges that are directed.

3.2.4 Layout

For visualization purposes, there are several possibilities as to how we can spread the nodes in a typically 2D or 3D image [7, 41–44]. Proper node placement can help in creating a clear and intuitive picture making it easier to understand the relationships between the nodes. On the other hand, the emerging pattern in the network can be hidden if a poor option is chosen. This is called network layout. In figure 3.2 we can see an example of all the students and relationships using a Multidimensional Scaling (MDS) layout [7].

3.2.5 Homophily

Homophily is the core reason why social network studies work. Individuals tend to form strong bonds with people who are similar to them by factors such as marital status, race, economics, nationality, common interests, and many more [45–57]. This is also the biggest challenge when interpreting data, as we cannot be sure if individuals who are

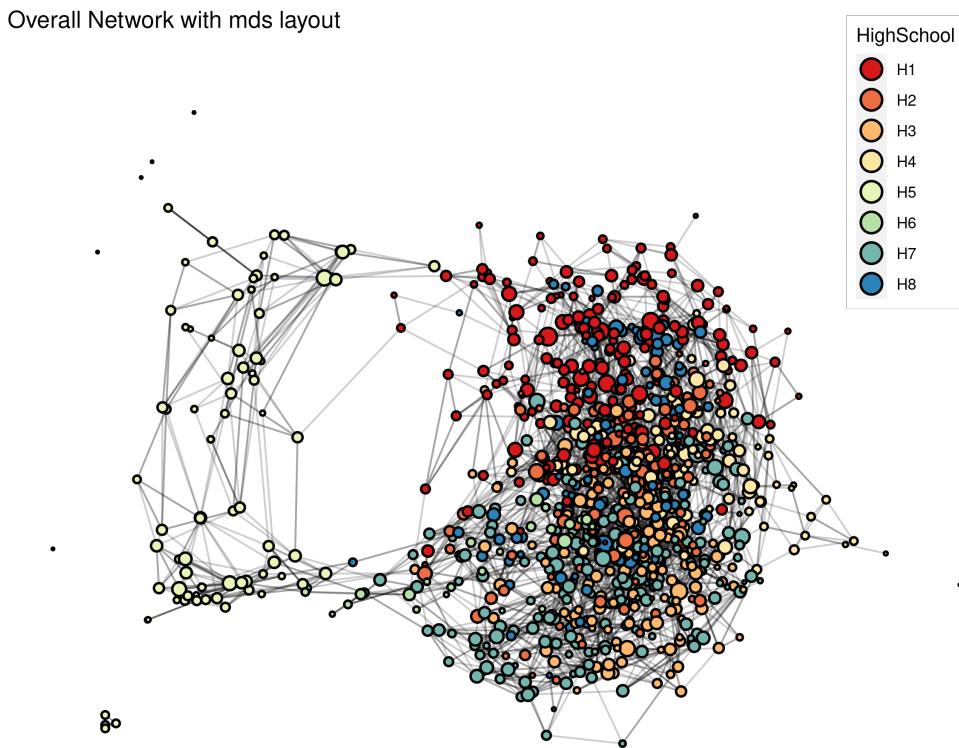


Figure 3.2: Fit Futures 1 (FF1) overall network with MDS layout [7]. Each student is displayed as a node represented as a circle of size proportional to the number of relationships. Each undirected friendship is displayed as an edge represented as a line between nodes. Each node is colored according to the high school to which the student belongs. MDS is a popular dimension reduction technique that tries to maintain similar nodes close to each other.

close to each other are actually influencing each other or simply sharing an environmental factor that influences everyone at the same time to no fault of the nature of their relationships.

Homophily is the ratio of, nodes that have an edge to another node that has the same property, against nodes that have an edge to a node of different property. The homophily value needs to be compared to another homophily value to gain some useful information.

3.3 *Staphylococcus aureus*

3.3.1 Introduction

The word "Staphilus" derives from the Greek "σταφυλόκοκκος", composed of "staphylé" meaning bundle, and "coccus" meaning grape. This refers to their bundle of grapes-like arrangement. "aureus" comes from Latin origin meaning golden, which is the golden-orange characteristic color of this bacteria as it is rich in carotenoid pigments. *S. aureus* was discovered in 1880 by Alexander Ogston who noticed a formation of bacteria in pus during a procedure he was performing [58]. Wounds caused by *S. aureus* infections were fatal for most patients until the 1940s when it was discovered that benzylpenicillin could cure such infections. But unfortunately, shortly after [59], *S. aureus* evolved into a penicillin resistance strain which became widespread by the end of the century. This led to the development of methicillin [60] in the 1960s, which was a better option to treat infections caused by the bacterium. However, again, the bacteria evolved to be antibiotic resistant, called *Methicillin-resistant Staphylococcus aureus* (MRSA). Once this strain was characteristic of the hospital, but today it is widespread (ranging from 2% to %80) in both human and cattle population [61], and thus it is important to understand the *S. aureus* social spread which motivated the writing of Paper A.

Nearly 30% of humans are carriers of *S. aureus* [62] which are usually present in the skin and the upper respiratory tract. Under normal circumstances the bacteria is harmless, but it can cause a wide range of diseases, ranging from minor skin diseases such as pimples or follicles the most common ones, to life-threatening ones such as pneumonia, endocarditis, and sepsis. *S. aureus* is in the top five most common intrahospital infections and is the most common cause of wound infection after surgery, causing around 500.000 hospital infections in the US alone [63], of which 10% end up in death-related to such infections from the non-antibiotics resistance strain alone [64].

3.3.2 *S. aureus* main characteristics

The mechanisms of the spread of *S. aureus*, as well as the severity of its associated illnesses, are quite diverse. It is important to understand the mechanism of action as well as the vector of infection of any pathogen to evaluate the social impact.

S. aureus is a Gram-positive bacterium capable of growing in both aerobic and anaerobic, and a variety of acidic or based places, although it prefers aerobic and neutral acidic environments such as the skin.

The *S. aureus* can have both a capsule and a slime layer depending on the strain. The *S. aureus* capsule inhibits phagocytosis as with many other bacteria capsules. The capsule is prone to contain adhesin proteins which help *S. aureus* adhere to the epithelium of the mucosa, such as skin, nasopharynx, oropharynx, gastrointestinal tract, and in neonates umbilical stump and peri-anal area. The *S. aureus* slime layer is prone to forming biofilms. [65]

The peptidoglycan in the cell wall in the *S. aureus* provides surface adhesion proteins that have a very special function. They adhere to the peptidoglycan cell wall (bacteria) and at the same time to fibronectin, fibrinogen, collagen, or elastin (human tissue). Technically, it helps the immune system recognize the bacteria which is why are called Microbial Surface Component Recognizing Adhesive Matrix Molecules (MSCRAMM). But in the *S. aureus* case Staphylococcal protein A (Spa) arrest antibodies by binding to the constant part of the Immunoglobulin G (IgG), preventing antibody-mediated immune clearance of the *S. aureus* [66]. Furthermore, this forms an antigen-antibody complex, which activates the classical complement pathway of the complement immune system, wasting it, and leading to hypocomplementemia which can further aggravate other conditions [67].

In *S. aureus*, Clumping factor proteins A (ClfA) and Clumping factor proteins B (ClfB) transform fibrinogen into fibrin. They both bind to fibrinogen and promote clotting, forming a shell around the *S. aureus*, which is the way *S. aureus*, a coagulase-positive bacteria that lacks endospores as any other, can actually make something similar to endospores which helps it hide from the immune system in highly localized surfaces [68]. This also serves as an adhesion protein that binds the peptidoglycan cell wall to other surfaces and tissues.

Toxic Shock Syndrome Type-1 (TSST-1) is a toxin which can be released by *S. aureus*. This toxin acts as a superantigen. Antigen Presenting Cells have major histocompatibility complex 2 (MHC2) that interact with other cells like T-cells via their CD4 protein. TSST-1 acts as a bridge between the two a hyperstimulates their response leading to a cytokine storm of Interleukin 1 (IL-1), Interleukin 2 (IL-2), Tumor Necrosis Factor α (TNF α), and Interferon gamma (IFN- γ). All of these proteins lead to an inflammatory reaction that acts on the skin creating a rash [69]. They also increase capillary permeability causing vasodilation of the blood vessels leading to both hypotension and hypovolemic shock. Finally, they also increase prostaglandins in the hypothalamus, which leads to fever.

3.3.3 *Staphylococcus aureus* diseases

S. aureus is usually harmless and will just colonize the skin and nasopharyngeal tract of the host. However, it is also an opportunistic bacterium that easily attaches to and infects many tissues and can develop much more serious complications there [70]. These diseases range widely and can be caused by either the bacteria or the toxins produced by them.

Skin lesions include superficial abscesses, folliculitis, furuncles, and carbuncles. Carbuncles can result in generalized sepsis and septic embolisms. *S. aureus* is the most common pathogen associated with wound infections and the most frequently isolated bacteria from chronic wound infections [71]. In particular, Staphylococcal scalded skin syndrome (SSSS) is a skin infection that mainly affects patients with weak immune systems. SSSS is characterized by blistering of the skin similar to a sunburn-like rash, and the skin may feel like it is scalded, leading to Nikolsky's sign. This last symptom can also be presented as bullous impetigo.

Catheter-associated infections develop from *S. aureus* being attached to medical equipment, forming a biofilm around it, leading to bacteremia [72]. This can develop further into pyomyositis, endocarditis, lung abscesses, brain abscesses, osteomyelitis, septic arthritis, ocular infections, or necrotizing pneumonia. *S. aureus* can also be introduced into the body due to poor cooking hygiene leading to food poisoning.

Several antibiotic resistant strains exist, such as MRSA, *Vancomycin-resistant Staphylococcus aureus* (VRSA), and particularly *Linezolid resistance in Staphylococcus aureus* (LZRSA) [73–79].

3.4 Inflammation

3.4.1 Introduction

In this study, we want to evaluate if the inflammation response is similar between individuals. Sharing an experiment of copying behaviors among friends can lead to similar immune responses, including inflammation outcomes. This is what motivated the writing of **Result II**.

Inflammation has 4 main characteristics: heat, pain, redness, and swelling. The combination of these may lead to a 5th one which is loss of function in the affected

area. Inflammation is a natural process that the body uses to fight infections and eliminate the cause of inflammation, clear out the area of elements that should not be there, and repair the tissue if damaged. Similar to fever, it has a bad name with the general population even for mild cases despite being a beneficial and necessary process for recovery. People tend to self-medicate in excess with antipyretics and anti-inflammatories which is counterproductive for both healing processes [80]. This process of acute inflammation is inherent to the natural healing process of an organism and overall, the natural pathways of inflammation do not pose a risk to the organism's life, and it is counterproductive to interfere with it, as such interference may ultimately impair the healing process in the long run. On the other hand, autoimmune reactions and chronic inflammations are the undesirable form of inflammation that may lead to lasting damage; often in the form of scar tissue.

3.4.2 Stimuli

In order to start an acute inflammation process it is necessary to provide the body with a stimulus, for example, pathogens, toxins, radiation, or physical trauma [81].

3.4.3 Clotting

In the event of an injury, it is imperative to promptly address the issue of bleeding in order to prevent fatality resulting from excessive blood loss.

The first step in blood clotting is the formation of a platelet plug at the injury area. Platelets possess specific receptors on their surface, such as glycoprotein Ib/IX/V, which allows them to adhere to the exposed collagen fibers, resulting in their adhesion to each other and the formation of a temporary seal over the injured site [82]. As platelets aggregate, they release von Willebrand factor (vWF) so they can stick together, and thromboxane reduces blood flow to the site of injury [83]. This forms a quick temporal fix that prevents further bacteria from entering the body and provides the basic structure for tissue repair.

Once the platelet plug has formed, a more stable blood clot is formed later on using proteins called clotting factors. These clotting factors work together to convert prothrombin, into thrombin, which in turn converts fibrinogen into fibrin. Fibrin forms a net that reinforces the platelet plug, creating the final stable clot.

3.4.4 Acute phase

Once the clot is in place, it is possible to activate vasodilation and bring in the immune system so it can deal with the infection. Leucocytes have external Patter Recognition Receptors (PRRs) in the cell surface which are activated in contact with Pathogen Associated Molecular Patterns (PAMPs) or Internal Damage Associated Molecular Patterns (DAMPs), which trigger the immune and inflammation response [84]. These PRRs are non-specific, meaning that the leucocyte does not know what causes the stimuli, just that something bad is happening and an immune response needs to happen to whatever it is. There is also no cell memory associated with the PRRs.

Additionally, some non-immune cells such as epithelial cells, endothelial cells, and some stromal cells can also express certain types of PRRs that can recognize viral components such as Toll-like receptors (TLRs) or RIG-I-like receptors (RLRs).

When PAMPs interact with a granulocyte they release histamines, bradykins, and eicosanoids that cause vasodilation in blood vessels and also open a gap in the endothelium releasing blood into the area close to where the DAMP activity is happening, which causes swelling. It also causes muscle relaxation which causes vasodilation (localized hyperemia). You get more blood in the area which turns the area red. It also helps endothelium cells to express more selectins which attract neutrophils to the inflammation site via extravasation (figure 3.3). Then neutrophils phagocytose the bacteria. Then dendritic cells present pieces of the bacteria to T-lymphocytes which activates the adaptative immune system if necessary.

3.4.5 Switching and resolution

Specialized pro-resolving mediators (SPMs) are produced to inhibit pro-inflammatory mediators and regulate neutrophils. This mechanism is done by the Lipid-mediator-class switching.

Lipoxins reverse the actions of the pro-inflammatory mediators and initiate tissue repair response [85]. Among many other things, they inhibit chemotaxis, transmigration, superoxide generation, NF-κB activation, generation of pro-inflammatory cytokines, suppress the production of Immunoglobulin M (IgM) and IgG antibodies, reduce the perception of pain due to inflammation, induce the production of elements that neutralize oxidative stress and oxidant-induced tissue damage and block the actions of some leukotrienes. [86]

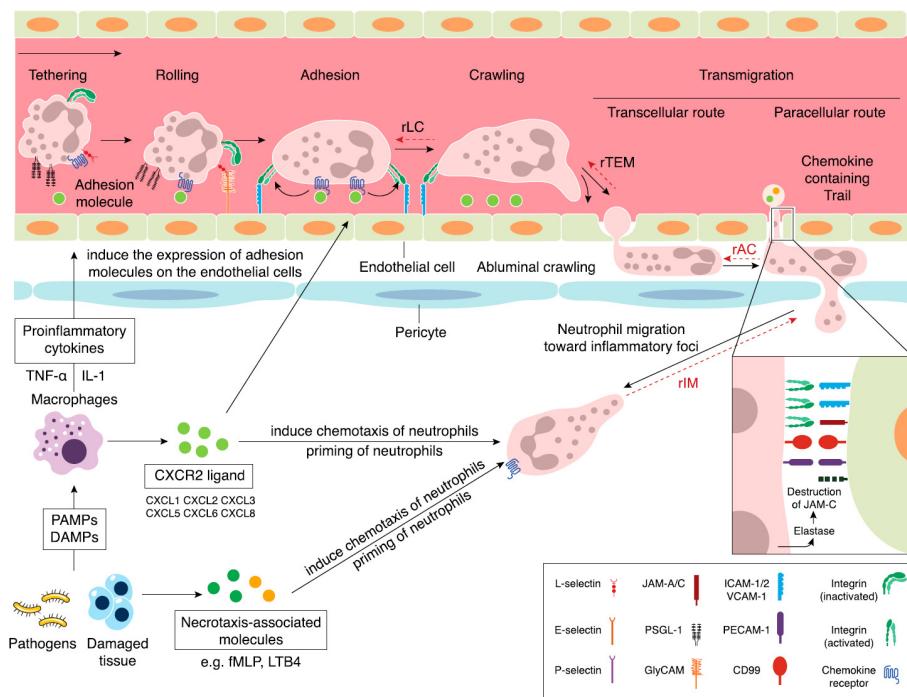


Figure 3.3: Overview of cell migration from a blood vessel to an inflammation site. Image reproduced with permissions from "Deep insight into neutrophil trafficking in various organs" [8].

Resolvins play an important role in resolving inflammation by promoting the clearance of cellular debris, bacteria, and other inflammatory mediators. They also inhibit neutrophil recruitment, decrease pro-inflammatory cytokine production, and promote tissue repair and regeneration [87]. The importance of resolvins lies in their ability to control the duration and intensity of inflammation, which is crucial for preventing the development of chronic inflammatory diseases. They are formed from the metabolism of omega-3 polyunsaturated fatty acids, in particular, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Humans convert alpha-linolenic acid (ALA) to EPA very inefficiently [87], so it is recommended to take food rich in EPA directly such as salmon, mackerel, herring, cod liver, some algae, and human milk. DHA can be converted from EPA but is recommended to also take DHA-rich food such as salmon, caviar, anchovies, mackerel, or herrings.

Protectins reduce inflammation induced by oxidative stress and inhibit the pro-apoptotic signal. Can potentially protect respiratory cells from viral infections. Blocks formation of pro-inflammatory prostaglandins inhibits platelet-aggregating by thromboxane thus blocking the platelet aggregation responses such as those described for *S. aureus*, and stimulate the efferocytosis [88, 89].

Maresins (**MA**crophage **mediator** in **R****E**Solving **I**Nflammation) are involved in resolving inflammation and allergic reactions, wound healing, apoptotic human neutrophils by human macrophages, reduced lung inflammation, suppress the production of IL-5 and IL-13, and reduce the production of LTB4 [90].

Eoxins are proinflammatory eicosanoids first described in 2008 [91] which are suggested to contribute to the inflammation of airways during allergies and some cancers [92]. They still have an unknown function in human physiology or pathology. But their production is stimulated in eosinophils by pro-inflammatory mediators Protecting D2 (PD2), Leukotriene C4 (LTC4), and Interleukin 5 (IL-5).

3.4.6 Tissue repair

Macrophages eat dying or dead cells which provide room for new cells [93]. They also secrete growth factors that promote the angiogenesis of temporal capillary vessels. Fibroblasts synthesize collagen in the area of interest. Mild damage in a tissue gets repaired to a normal state, while in severe damage the tissue is replaced by a non-functional fibrous scar.

3.4.7 Chronic inflammation

If everything goes well, the infection has been neutralized, and the inflammation has subsided. However, sometimes errors can occur. Typically this involved not being able to clear the site of inflammation from the cause. For example DAMPs or any other bacterial debris [94]. In worse cases, external bodies such as undetected wood splints, or metal allocated inside the muscle cannot be removed surgically.

Dysregulation of cytokine signaling can result in excessive production of pro-inflammatory cytokines such as TNF α [95], IL-1 [96], or Interleukin 6 (IL-6) [97]. Otherwise, a failure or delay of activation of the SPMs mechanisms. Finally, autoimmune diseases such as celiac disease, rheumatoid arthritis, lupus, and many others lead to chronic inflammation.

3.5 Vitamin D

3.5.1 Introduction

Vitamin D is crucial in any population, but in the Arctic, it has a special interest due to the lack of sun exposure which limits the availability of this vitamin. If friends share similar vitamin D levels, then it is possible to promote behaviors that enhance vitamin D absorption which motivates the writing of Paper B.

The human body requires what is called essential nutrients, which are compounds that the body cannot synthesize by itself, or is unable to synthesize in large enough quantities. These essential nutrients consist of macro-nutrients, vitamins, minerals, choline, and water [98].

Vitamins are organic molecules that the body needs in small quantities for correct metabolism. They are presented in two groups, water-soluble vitamins, and fat-soluble vitamins. Water soluble means they dissolve in water, while fat soluble means that they dissolve in fat. Vitamin D, along with vitamins A, E, and K, belongs to the fat-soluble group, meaning that they are absorbed through the intestinal tract with the help of lipids. Luckily, vitamin D is already present in fat-rich foods such as salmon. Humans need a constant intake of water-soluble vitamins as the body is unable to store them, except for B9 (folate) and B12 (cobalamin) which are not stored either but can last for weeks to years respectively.

There are two primary functions for vitamin D, to absorb calcium and phosphate from the gut into the blood; and to inhibit Parathyroid hormone (PTH) production. There are plenty of secondary functions such as immune homeostasis, which showed a worrisome trend during the COVID-19 epidemic in which people with lower vitamin D levels lead by almost 90% of total deaths [99, 100]

3.5.2 Sources and metabolism

There are two methods by which your body obtains Vitamin D, sun exposure (pre-vitamin D3) and food intake or dietary supplements (vitamin D2 and D3) [101]. Regardless of intake method, vitamin D needs to undergo two chemical transformations known as hydroxylation to be activated and do its functions. The first one occurs in the liver and transforms vitamin D into 25-hydroxyvitamin D (25(OH)D), using 25-hydroxylase. This first form of vitamin D is the variable that we measure in the blood serum later

on. The second hydroxylation happens in the kidneys and forms 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$), using $1-\alpha$ -hydroxylase, which is the final and physiologically active form of vitamin D. This form is known as calcitriol. If calcitriol becomes excessive, then it is converted to 24,25-dihydroxycholecalciferol, which is less active. This prevents hypervitaminosis D, and it is why this condition is very rare [102] unless a person takes an overwhelming amount of vitamin D supplements [103].

Both vitamins D2 (ergocalciferol) and D3 (cholecalciferol) raise $25(\text{OH})\text{D}$ levels. The metabolism and actions of vitamins D2 and D3 are identical, and they only differ in the chemical morphology present in their side-chain structure. Evidence suggests that vitamin D3 increases $25(\text{OH})\text{D}$ levels greater and longer than vitamin D2 [104–107]. Dietary supplements of $25(\text{OH})\text{D}3$ are three to five times as potent as vitamin D3 supplements [108, 109]. In any case, all forms of dietary vitamin D are absorbed in the small intestine via passive diffusion using intestinal membrane carrier proteins [110]. As stated before, the presence of fat helps the diffusion and absorption of vitamin D, although some vitamin D can still be absorbed without fat.

3.5.3 VDR

Lastly, calcitriol needs to enter the cells; this is where the Vitamin D receptor (VDR) comes into play. This protein is mostly found in the cells of the small intestine, immune system, kidneys, and bones. Calcitriol then binds to VDR, which forms a protein complex that enters the nucleus of cells and binds to DNA, up or down-regulates the expression of hundreds of genes [111, 112]. This includes calcium absorption (promotes calbindin), bone formation, cell growth [113], and immune function. VDR regulates the production of cytokines in the immune system, generally acting as an anti-inflammatory agent, facilitating humoral response, and leading to homeostasis. In figure 3.4 we see an overview of these functions.

3.6 Over-the-counter medicine

3.6.1 Introduction

OTC medicine [114] refers to a type of medication that is sold without the need for a prescription and can be acquired even outside of pharmaceutical outlets such as supermarkets. These types of medicine have a low dosage of the active agent and are used to alleviate common symptoms such as pain, fever, cough, allergies, and digestive issues

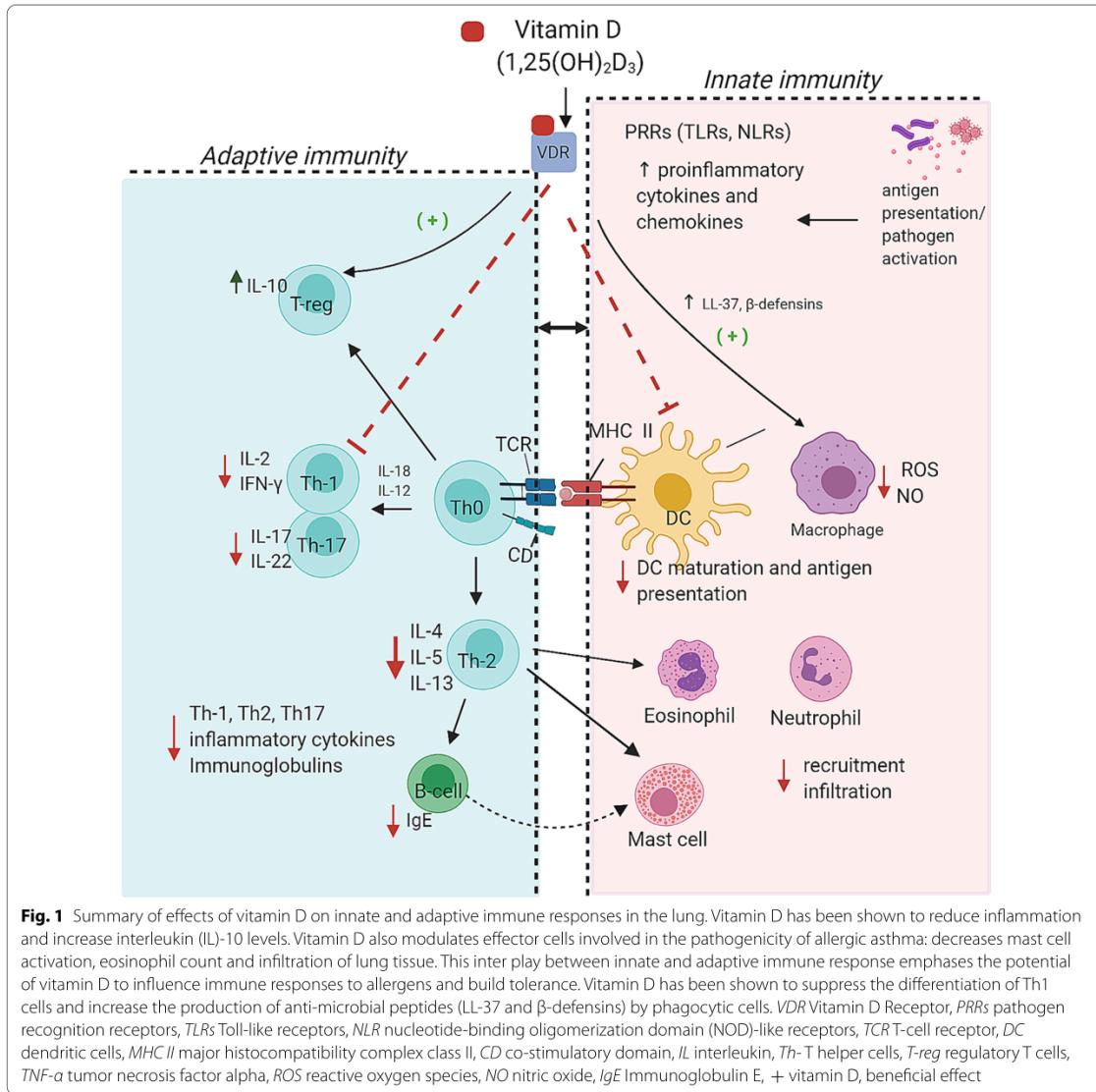


Figure 3.4: Vitamin D effects on the immune system. Figure reproduced under CC4.0 license from "Recent advances in vitamin D implications in chronic respiratory diseases" [9].

OTC are fairly safe when used in moderation and responsibly. However, this is not always the case. About 16% of the population misuse these medicines, and up to 7% are addicted to them [114–117]. Common reasons for its use are the false belief that if taken more the symptoms will go away faster, or to the contrary, for self-harming purposes [114]. In Norway [118], teenagers report using these drugs mostly for physical pain, to alleviate stress and fatigue, due to familiar conflicts, and to appear socially successful; while the common user is a person with constant pain, binge drinking, having school problems, bad sleeping habits, lower life ambitions and high spare time. About 55% of OTC medicines are sold in non-pharmaceutical outlets [118].

In this section, a short summary of common OTC medicines will be listed in addition to their function, mechanism of action, possible side effects, and how they are used as recreational drugs [119].

3.6.2 Analgesics

Analgesics are a class of drugs commonly known as painkillers. They reduce or block the perception of pain signals in the brain. Nonsteroidal anti-inflammatory drug (NSAIDs) usually overlap their effect with analgesic medicine but will be discussed in the antiinflammatories section.

The most common active component of analgesics is paracetamol (acetaminophen) [120]. This is metabolized in the liver and flushed into the kidney fairly quickly. About 2% of it transforms into N-acetyl-p-benzoquinone imine (NAPQI), which remains in the liver for a longer time before it also moves into the kidneys. However, NAPQI is toxic. When taken in a low amount, the liver can detoxify NAPQI quickly enough before it becomes a serious problem by combining it with a molecule called glutathione. Problems arise when analgesics are taken in higher doses or at a higher frequency, the liver may become overwhelmed and unable to detoxify all of the NAPQI, leading to liver damage and potentially liver failure.

In contrast, non-OTC analgesics are usually opioids such as morphine. They work by binding to specific receptors in the brain and spinal cord called opioid receptors [121]. Activating these receptors blocks the transmission of the most severe pain signals. However, they are at risk of addiction and their use is severely restricted.

Analgesics are not used as recreational drugs directly but are used in combination with other substances such as alcohol or cannabinoids [119].

3.6.3 Antihistamines

Antihistamines are a class of medications that are commonly used to treat allergic rhinitis and allergic-like symptoms. They work by blocking histamine, hence their name. Histamine is released when allergens bind to mast-cell-bound Immunoglobulin E (IgE) antibody sites [122]. This is commonly known as an allergy and is the mechanism of bronchial smooth muscle contraction, urinary bladder contractions, vasodilation, visceral hypersensitivity, itch perception, urticaria, sneezing, hyper-secretion from glandular tissue, and nasal congestion due to vascular engorgement.

Different antihistamine medications can cause both vasoconstriction and vasodilation. In general, vasodilation may be more effective at relieving symptoms such as congestion and mucus production, while vasoconstriction may be more effective at reducing inflammation and swelling. But both cases can be detrimental. Vasoconstriction can increase blood pressure in the heart and reduce blood flow in the kidneys. For patients with decreased kidney functionality or hypertension, this would be dangerous. Vasodilation increases blood flow, which is generally beneficial for normal kidney function. However, it is detrimental in cases when the patient is incapable of filtering waste, and excess fluid from the blood would lead to a buildup of toxins and fluid in the body. Lastly, worth mentioning that the first generation of antihistamines developed during the 1930s have a detrimental flaw and they tend to cross the brain-blood barrier [123]. The blood-brain barrier is a specialized system of blood vessels that helps to protect the brain from harmful substances and toxins.

The effects of drug abuse related to antihistamines have a huge variety, but as a general rule, they are used as vasodilators, which promote a calming and sedating effect. They can enhance the effect of other substances such as making opioids more hallucinogenic, especially the first generation [119].

3.6.4 Antiinflammatories

NSAIDs drugs such as ibuprofen work by inhibiting the production of prostaglandins. Prostaglandins cause blood vessels to dilate, which can increase blood flow to the affected area and cause redness and swelling. They also sensitize nerve endings to pain, which can cause pain and discomfort. NSAIDs work by inhibiting the activity of an enzyme called cyclooxygenase (COX), (subdivided into COX1 and COX2) which is responsible for the production of prostaglandins (PG) [124].

NSAIDs can be divided broadly into three categories, COX1 inhibitors, COX2 inhibitors, and both COX1 and COX2 inhibitors. Prostaglandins PGE2 and PGI2 participate in the synthesis of protective mucus and gastric flow, which is why a normal side effect of COX1 inhibitors is gastrointestinal bleeding and ulcers [124]. COX1 also participates in the production of thromboxane which promotes platelet aggregation, which is why antiinflammatories such as aspirins can cause an increase in bleeding. On the other hand, prostaglandins PGI2 and PGH2 are vasodilators and share COX precursors with thromboxane which is also a vasoconstrictor. Simply put, there must be an equilibrium between COX1 (vasoconstrictor) and COX2 (vasodilator). NSAIDs that inhibit COX2

increase blood pressure which can lead to heart infarction [124]. These side effects can be mitigated with the usage of prostaglandin analog medicines.

Due to their vasoconstriction nature, these medicines can be used as stimulants, which can also induce psychotic symptoms, paranoia, and visual hallucinations. [119]

3.6.5 Cough syrups

Cough syrups are used to stop unwanted coughing which may cause discomfort, or even physical injuries, in the upper respiratory tract. Their mechanism of action is not fully understood but their effects are accomplished by reducing the signaling between the laryngeal nerves and vagus nerve [125].

The three main antitussive components are codeine, Dextromethorphan (DXM), and benzonatate [126]. Codeine breaks down into codeine-6-glucuronide and morphine, which stimulates the μ -opioid receptors [121] causing euphoria, constipation, and also cough suppression. DXM is the principal component in OTC medicines, and it has similar side effects of codeine but in the form of hallucinogenics, and in particular as a dissociative. Benzonatate is a non-narcotic drug that works as a local anesthetic in the whole respiratory tract.

Due to their action on the peripheral nervous system, the main side effect of these drugs is reduced consciousness in the form of drowsiness. In higher dosages, it can lead to hallucinations, paranoia, perceptual distortions, delusional beliefs, ataxia, and out-of-body experiences [119].

3.6.6 Antidiarrheals

The main component of these drugs is loperamide. Loperamide works by binding to peripheral μ -opioid receptors in the gastrointestinal tract [127]. It inhibits the release of acetylcholine and other neurotransmitters that stimulate the contractions of the intestinal wall. This leads to a decrease in the motility of the intestines, which slows down the passage of stool and reduces the frequency and urgency of bowel movements. This also allows for the gastrointestinal tract to have more time absorbing fluids, increasing the hardness of the fecal matter.

Similar to antitussive medications, antidiarrheals relax the peripheral nervous system. Thus, these drugs are used also as opioids, to alleviate symptoms of opioid withdrawal, or as a psychoactive. [119]

3.7 Machine learning

3.7.1 Introduction

Random Forests (RF) and Artificial Neural Networks (ANNs) are both popular machine-learning algorithms used for classification and regression tasks [128]. RF combines multiple decision trees to make predictions, and ANNs simulate the behavior of neurons in the brain. RF randomly selects a subset of input features for each tree, whereas ANNs use all input features available in the data. RF is more straightforward to interpret than ANNs, which have more complex interconnections and act more like a black box model. However, ANNs can reproduce better complex and non-linear relationships between input features. RF is prone to overfitting. ANNs share the same problem if the model is too complex or the training data is not large enough. ANNs also require tuning various hyperparameters to achieve a good prediction rate.

There are other classical machine learning techniques which could be applied. Support Vector Machines (SVM) [128] are also good with high non-linear dimensional data and have good generalization, but are computationally intensive and in particular difficult to interpret and visualize. K-Nearest Neighbors (KNN) [128] could be potentially used to classify subjects into different strategies, each being the optimal strategy for achieving healthy weight (i.e.: Smoking less, having more friends, etc.), but it goes a bit beyond our objective of trying to explain what influenced a person's BMI value the way it is. Naive Bayes is very simple, quick, and easy to interpret, but it assumes independence between variables which in our case is too much of a stretch in the assumptions. Gradient boosting can be used in future work when we lay out the basics for our models. ANN and RF were finally selected as the most relevant models for [Result III](#).

3.7.2 Interpretability

An important concept is the interpretability aspect of the machine learning models [129]. It is crucial as machine learning is increasingly being used in critical areas such as health-care, finance, and law where clear explanations are essential. In general, methods offer easy interpretability in exchange for lower accuracy. The key concept in our context is feature importance, which aims to identify the variables that have the most influence on the model's predictions. For example, it's important to identify which variables are most important for predicting the risk of heart disease; variables such as age, blood pressure, and cholesterol levels may be more important than gender, BMI, or occupation.

SHAP values

SHapley Additive exPlanations (SHAP) computes Shapley values [130], which is a mathematical concept from Cooperative Game Theory, to explain the contribution of each input feature to the final prediction of the model. SHAP can be used on any machine learning algorithm and is easy to interpret, but it requires a large number of samples to properly capture the interactions of variables. RF in particular has the advantage of having a very easy-to-interpret model.

Mean Decrease in Impurity

Mean Decrease in Impurity (MDI) [131] is a measure used in random forests to quantify the importance of each feature in predicting a target variable. The MDI is calculated by measuring the importance of each variable, in each tree, and calculating how the impurity is reduced. When a variable is used to split a tree node, it reduces the impurity of that node, and the reduction in impurity correlates to the importance of that variable. The MDI for a feature is calculated by averaging the reduction in impurity across all trees in which that feature is used. Higher MDI means more importance.

3.8 Statistical Analysis

3.8.1 Contingency tables and Pearson X^2 test

Contingency tables are used to determine if the total number of samples in a combination of two categorical variables (i.e.: Sex and BMI), happens to be within the range of the values that we would expect by chance [132]. Several tests can be performed to determine if these combinations are suspicious or not. One in particular is the Pearson Chi-square test which uses a Chi-square distribution for a specific degree of freedom. The degree of freedom is related to the number of variables in the calculation and they represent the number of independent pieces of information available to estimate or calculate statistics. The Chi-square value is calculated by taking the sum of the squared differences between the observed and expected data, dividing by the expected data, and then multiplying that result by the number of variables. The resulting value is compared to the values in the Chi-square table to determine if the null hypothesis can be rejected or not.

If the p-value of the analysis is significant, it means that some combinations of variables are suspiciously high or low. Each combination can, later on, be tested using a simple binomial test to highlight values far away from the expected ones.

3.8.2 Logistic regression

Logistic regression is a type of statistical analysis used to predict the probability of an event occurring based on a set of variables [133]; in our case, we use many results to tell what the probability of a subject having an effect as the number of friends increases or decreases. Is named after the logistic function which takes an S-shaped curve that can take any input value and map it to a value between 0 and 1, representing the probability of an event occurring. It is primarily used when the dependent variable is categorical or binary, such as yes/no, true/false, or success/failure.

In logistic regression, the odds ratio tells us how much more likely it is for the dependent variable to occur compared to not occurring, given a change in the independent variable. Probability and odd ratio are not directly interchangeable because they have different scales and have a non-linear relationship, but they can be approximated by:

$$\text{Probability} = \text{odds}/(1 + \text{odds}) \quad (3.3)$$

3.8.3 Autocorrelation models

An autocorrelation model is a statistical model that measures the relationship between a variable and its past values. This technique is commonly used in time-series analysis to identify patterns and trends over time [134]. In the context of network analysis, these models [135] strive to find how a network has changed until it finds an equilibrium point at the current time. We aim to find the ρ coefficient in the formula:

$$Y(t+1) = \rho W_n Y(t) + X\beta + \varepsilon \quad (3.4)$$

W is a weighted matrix of friends, which indicates who influences whom. X is the explanatory variable (sex, BMI, smoke...), and β is a vector of coefficients the same as in regular linear regression. Symbol ε is a random error noise vector. Y is the dependent variable vector which varies over time (t). This equation converges to a common value as t is increased. The ρ coefficient represents how much importance has the influence of friends, which ranges typically from 0 to infinity although negative values are also valid depending on the context. A value close to 0 would mean that friends have no influence. Negative values would indicate that friends influence others into doing the complete opposite, which could make sense for example if the explanatory variables are mutually exclusive and encoded with dummy variables.

Chapter 4: Methodology

4.1 Fit Futures

The Fit Futures (FF) study [136] is a cohort with repeated health surveys among high school students in the Norwegian municipality of Tromsø and the neighboring municipality of Balsfjord. This dataset is the main dataset used across all results of the thesis. All first-year high school students in Tromsø and Balsfjord were invited. FF1 was conducted from September 2010 to May 2011 for 8 months. FF1 included students from eight schools consecutively. A total of 1117 youths were invited 93% attended, 508 girls (48.9%), and 530 boys. The age ranges from 15 to 28 years old, with 822 (79.2%) being 16 years old or younger, and 52 (5%) older than 18 years old. Older students with special educational needs or mental disabilities have the right to study at the high school level in Norway. In figure 4.1 we can see the geographical distribution of the schools and in table 4.1 information specific to each school.

Fit Futures 2 (FF2) is a follow-up survey conducted from November 2012 to June 2013. FF2 invited all participants in FF1 and all new students from the third year at the eight high schools. Altogether 870 high school students were recruited in the FF2 study, and 78% of these attended both surveys. In the papers comprising this thesis, we only used FF2 anthropometrical data. However, FF2 included the same variables present in FF1, but we did not have access to this data. In FF2, 694 students (66.9% of the FF1 total) completed the anthropomorphic measurements, 378 girls (54.5% of total participants), and 316 boys. Some students in the vocational training program did not get permission from work to attend the FF2 follow-up measures, which contributed to lowering the total student count in the follow-up study.

In FF1 and FF2, the participants had a one-day visit to The Clinical Research Unit at the University Hospital of North Norway (UNN), which included clinical examinations, microbiological samples, blood samples, a web-based general questionnaire (chapter 7), and an interview [137]. All procedures were performed by trained research study nurses.

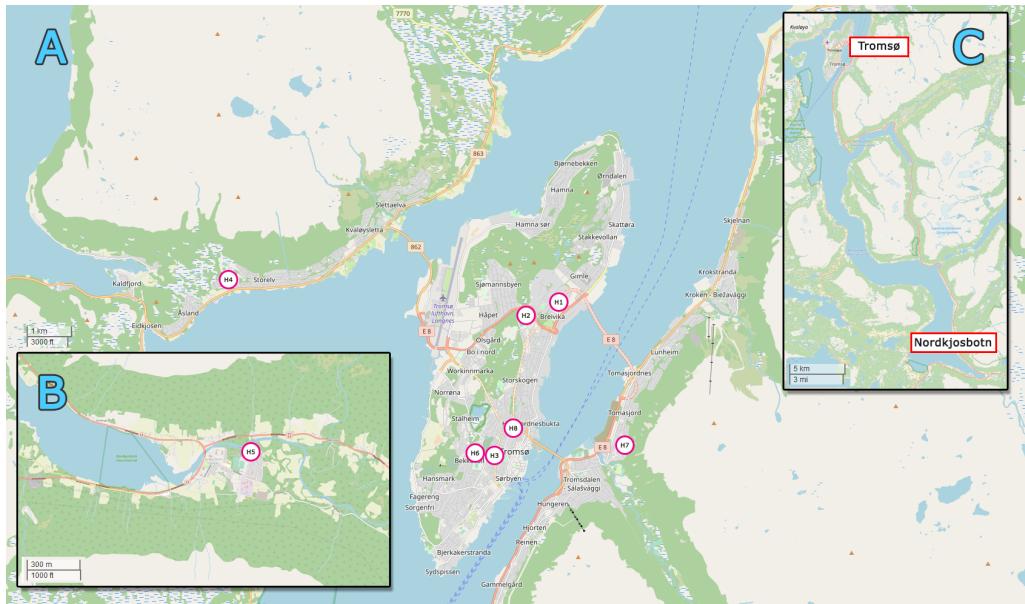


Figure 4.1: Geographical location of all eight high schools included in the Fit Futures study. "A" refers to the area around Tromsøya, and "B" is the area in the town of Nordkjosbotn (Balsfjord). "C" shows the distance between "A" and "B".

FF11 and FF12 refer to short follow-ups performed during the FF1 period. In these sub-surveys, not all the data was gathered again; only a sub-sample such as the swabbing of the *S. aureus*.

4.1.1 Social network assessment

The social network was constructed based on the following questions in the interview. These were written and answered in Norwegian, here we provide the English translation: “*Which students have you had the most contact with the last week? Name up to 5 students at your own school or other schools in Tromsø and Balsfjord.*”. Reciprocity in the nomination was not mandatory. For each of the nominations, five “yes/no” questions assessed the type of contact they had with their nominations: “*Do you have physical contact?*”, “*Are you together at school?*”, “*Are you together at sports?*”, “*Are you together at home?*”, “*Are you together at other places?*”. This resulted in five social networks: Physical Network, School Network, Sports Network, Home Network, and Other Network. Adding all the relationships together formed a sixth network that was called the Overall Network. Illustrations of all networks are presented in figure 4.2.

Not 100% of the students participated in the study, and some of the relationship information between them is lost (table 4.2). The final analysis shows that some of the lost 134 IDs, were very popular, with up to 9 friends nominated.

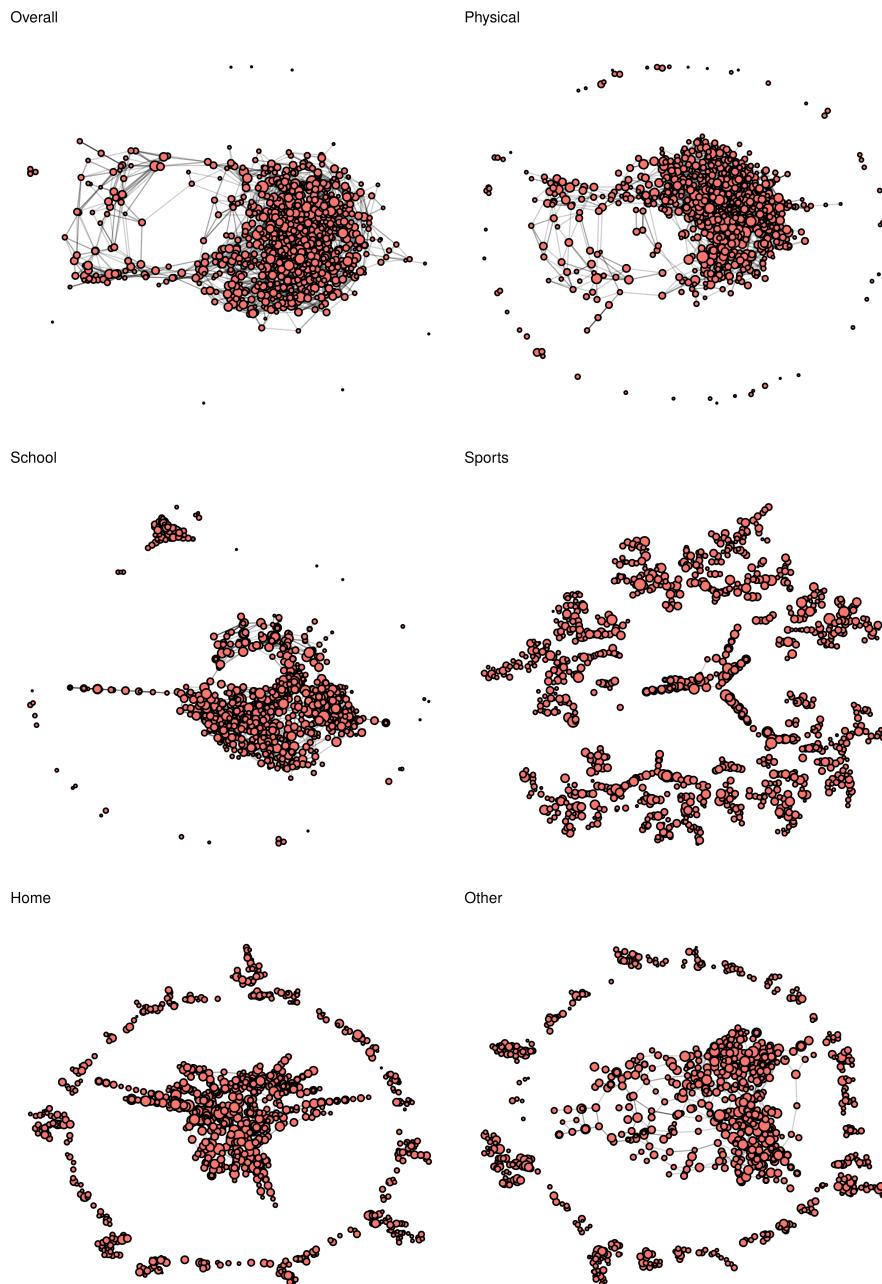


Figure 4.2: All networks in FF1 following a MDS layout. Each student is represented by one node in the network. Each relationship is represented by an undirected edge, i.e., a line, in the network.

To evaluate if the friends mentioned were representative of the participant's social network, the following question was asked: "*To what degree does this table of friends give an overview of your social network? Please indicate on a scale from 0 (small degree) to 10 (high degree).*" Nominated friends that did not participate in FF1 were excluded from the analysis ($n=134$). In figure 4.3 we can see a histogram with all the answers.

Table 4.1: Information with the school names, study program, the total number of students in FF1, astronomical season, and whether a significant amount of students' blood samples were taken during the polar night.

ID	Name	Studies program	FF1 Students	Extraction	Polar night
H1	Breivika videregående skole	Vocational	207	Autumn	No
H2	Breivang videregående skole	Vocational and General	142	Autumn	Yes
H3	Kongsbakken videregående skole	Vocational and General	168	Winter	No
H4	Kvaløya videregående skole	Vocational and General	98	Spring	No
H5	Nordkjosbotn videregående skole	Vocational and General	85	Spring	No
H6	Norges Toppidrettsgymnas Tromsø	Sports	26	Spring	No
H7	Tromsdalen videregående skole	Sports and General	192	Winter	Yes
H8	Tromsø maritime skole	Vocational	120	Winter	Yes

Table 4.2: Summary of lost connections at data cleaning.

Concept	Total	Relative
Total IDs:	1177	100 %
- Total Deleted IDs:	139	11.81 %
- Total Remaining IDs:	1038	88.19 %
Total Edges:	4125	100 %
- Total Deleted Edges:	473	11.47 %
- Total Remaining Edges:	3652	88.53 %

4.1.2 Host risk factors

All questions related to sex, use of recreational drugs, dietary habits, chronic diseases, medication usage, sport frequency, sedentism, and so on, are self-reported using a web-based questionnaire.

4.1.3 Hormonal contraceptive

Information on current hormonal contraceptive use was obtained from the interview. Hormonal contraceptives (HC) were categorized into combination contraceptives and progestin-only contraceptives. The combination contraceptives were further divided into groups according to high and low ethinylestradiol daily dosage. High dosage was defined as HC containing $\geq 30 \mu\text{g}$ ethinylestradiol. Low dosage was defined as contraceptives containing $\leq 30 \mu\text{g}$ ethinylestradiol. The classification for each brand can be seen in table 4.3.

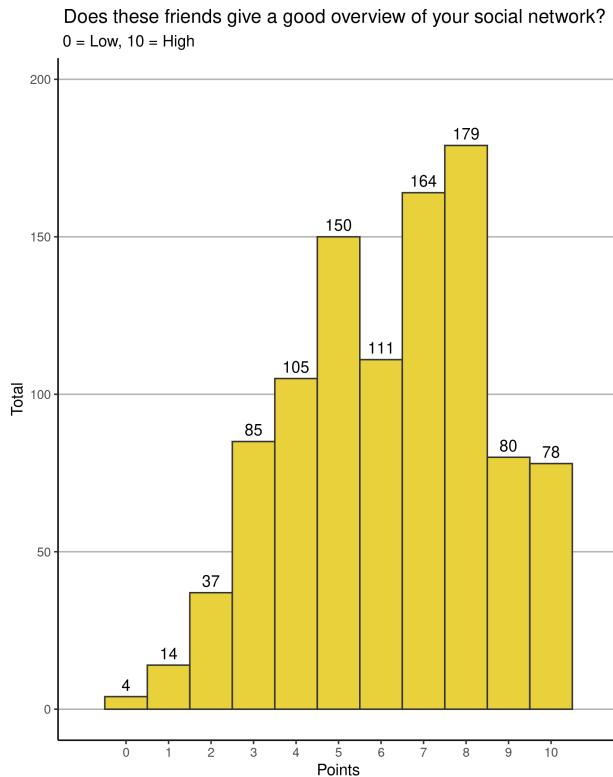


Figure 4.3: Histogram with all the answers to the question: “*To what degree does this table of friends give an overview of your social network? Please indicate on a scale from 0 (small degree) to 10 (high degree).*”

Table 4.3: Types of hormonal contraceptives classification and their respective brands.

Hormonal type	Contraceptive brand
Non-hormonal	Condoms
Progestin only	Cerazette Nexplanon Depo-provera Implanon
Low Estradiol	Mercilon Yasminelle Loette 28 Nuvaring
High Estradiol	Marvelon Yasmin Microgynon Oralcon Diane Synfase Evra Zyrona
Unknown	Any other brand/type

4.1.4 *S. aureus* assessment

A first set of nasal and throat swab samples was taken at the research center, and a second set of samples was taken at school after a mean interval of 17 days. All 1038 students were sampled on both occasions, the first batch contained 1028 valid samples, and the second batch 988. A NaCl (0.9%)-moistened sterile rayon-tipped swab rotated three times with gentle pressure was used to sample both vestibule nasi (nose sample), and an additional swab was used to sample both tonsillar regions (throat sample). The swabs were immediately placed in a transport medium (Amies Copan, Brescia, Italy) and stored at 4°C for a maximum of 3 days. All samples were analyzed at the Department of Microbiology and Infection Control, UNN, both by direct culture [138] and enrichment broth (Bacto Staphylococcus medium broth, (Difco Laboratories, Sparks, MD, USA - [139]), using blood agar for growth control (Oxoid, UK) and chromID-plates (SAID) for *S. aureus* detection (bioMérieux, Marcy l'Etoile, France). A summary of these methods can be found in the supplementary materials. The growth of any bacterial colonies on agar plates was registered as a valid culture. The most dominating *S. aureus* colony type was frozen at -70°C in glycerol-containing liquid media after confirmation by Staphaurex plus agglutination test (bioMérieux, Marcy l'Etoile, France).

From these results, *S. aureus* nasal or throat persistent carriage was defined as having two *S. aureus* positive cultures for each niche respectively. [140, 141] Two definitions of *S. aureus* persistent carriage was used in the analysis; one based on direct culture, and one based on enrichment broth. All results for every possible combination between the first or second sample, nasal or throat, direct culture or enrichment broth, and so on, can be found in figure 4.4.

4.1.5 SPA typing

SPA-typing is a technique used to identify the *S. aureus* strain. The gene encoding Spa is highly variable among strains of *S. aureus*, making it a good target for distinguishing different types of bacteria [142]. The technique involves targeting the Spa located in the cell wall are described in the supplementary materials.

For the analysis of *S. aureus* genotype, only data from throat isolates were available ($n = 746$). All *S. aureus* isolates from throat samples were subjected to spa-typing. The frozen cultures were inoculated on blood agar (Oxoid) and incubated overnight at 37°C. Two or three colonies were transferred to 200 µl sterile H₂O and vortexed. The isolates were later spa-typed [143].

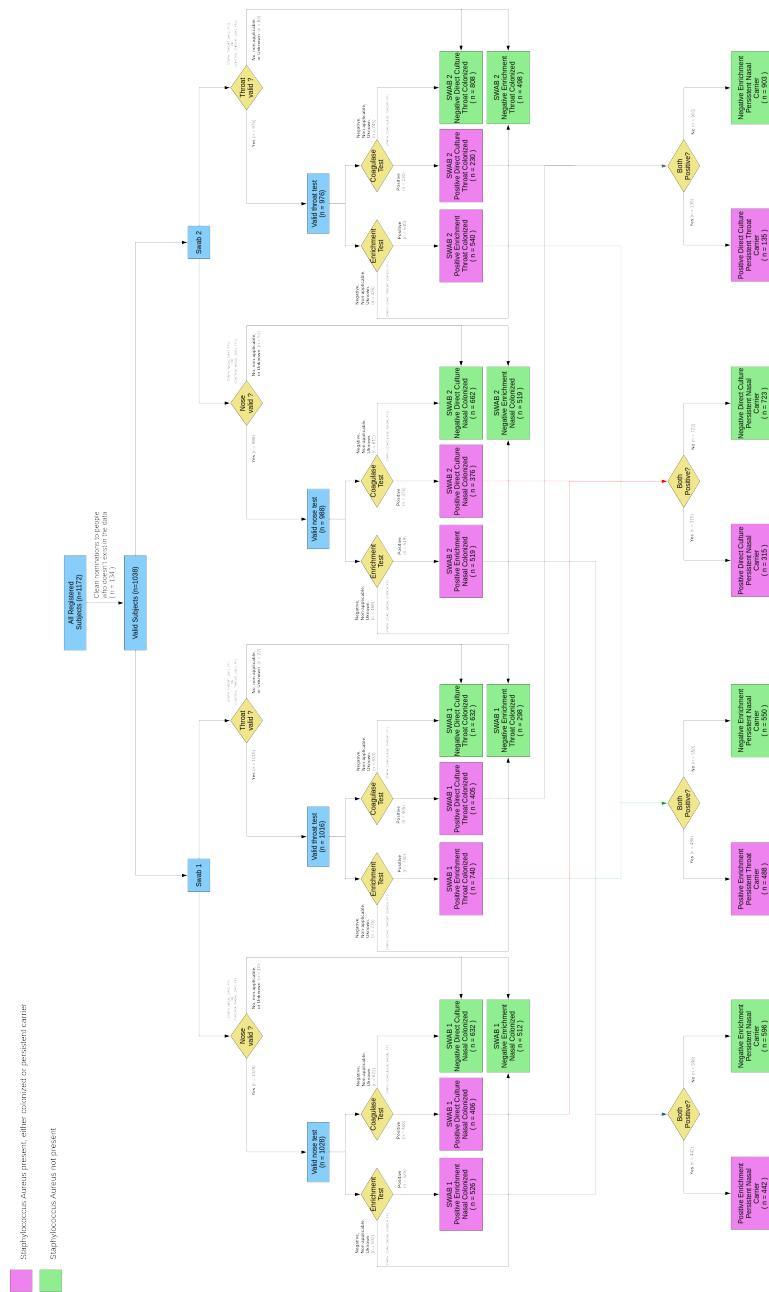


Figure 4.4: All the *S. aureus* combinations. A PDF version of this image can be found at the GitHub repository: <https://github.com/rafanozal/PhDThesis/blob/main/Images/carrierDefinition.pdf>

4.1.6 Anthropometry assessment

All anthropometric measurements were measured on an electronic scale with participants wearing light clothing and no footwear. BMI is calculated as weight (kg) divided by the squared height (m^2) with no correction for sex or age. FF1 has a total of 1034 valid samples, and FF2 has a total of 694.

The BMI comes as a real number and we categorize it following the World Health Organization (WHO) definition [144]. "Underweight" if the BMI is lower than 18.5, "Healthy" is above 18.5 and below 25, "Overweight" is between 25 and 30, and "Obese" is greater than 35. The new column is a categorical variable with this information for each person.

The WHO also provides BMI-for-age growth charts that take into consideration an individual's age and sex to determine their BMI percentile. A BMI percentile below the 5th percentile is considered underweight, while a BMI percentile between the 85th and 94th percentiles is considered overweight, and a percentile above the 95th percentile is considered obese. This definition is NOT used since being a relative respects an average rather than a constant value (i.e.: a student being the less obese of a group of people does not make the student not obese); instead, a constant reference point is used as described in the previous paragraph for better comparison across time.

4.1.7 Vitamin D assessment

Blood samples were collected by nurses at the UNN, centrifugated, and plasma serum was frozen at -70°C in the Biobank at the UiT: The Arctic university of Norway (UiT). All samples ($n = 890$) were sent to the Hormone Laboratory, Haukeland University Hospital, Bergen, Norway; and analyzed by high-pressure liquid chromatography-mass spectroscopy (LC-MS/MS). A sample from all blood vials was reanalyzed at University College Cork, Cork, Ireland, by LC-MS/MS again as a part of the Vitamin D Standardization Program (VDSP) [145], and standardization was applied to the rest of the samples [146]. 25(OH)D was used as a marker for vitamin D levels. This combines both sources of provitamin D + UVB, and D₂+D₃ from diet. It has a longer half-life span in blood than other available metabolites. Both 25(OHD)₂ and 25(OHD)₃ were measured at the same time.

4.1.8 OLINK Target 96 Inflammation

Serum levels of 92 proteins were analyzed at the Clinical Biomarkers Facility, SciLifeLab, (Uppsala, Sweden), using the Target 96 Inflammation panel from Olink Holding AB (Uppsala, Sweden) [147]. A detailed description of the significance of each marker, alongside the mathematical significance of the values, can be found in the supplementary materials. A total of 936 samples were analyzed this way.

4.1.9 Simulations

Bootstrapping is a statistical technique used to estimate the variability of a sample statistic without making any assumptions about the underlying population. To determine whether there is bias within the relationships in a network we use bootstrapping simulating 1000 networks using a similar approach to previously described non-parametric tests [148]. This consists of counting how many relationships connect two nodes with the same attributes in our network (i.e., *S. aureus* carrier with *S. aureus* carrier) and comparing this number with the same number given by the simulations. In figure 4.5 we can see an example of a real network, a simulated one, an arbitrary node attribute distribution, and the same-to-same relationships in each.

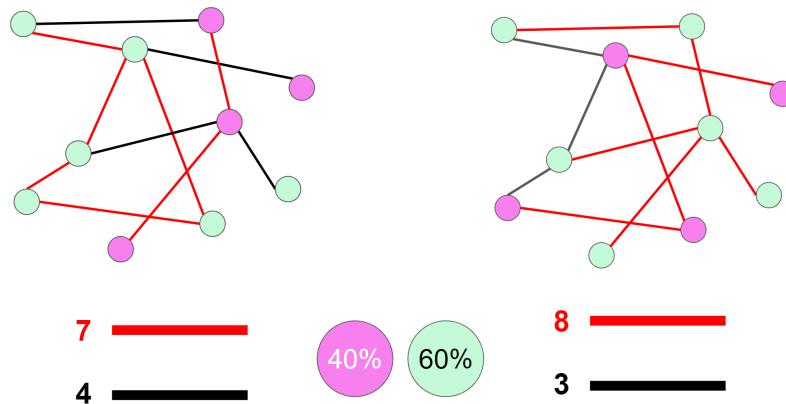


Figure 4.5: In this figure we see two isomorph networks with the same layout. On the left, we have a representation of a real network. On the right, is a simulated network. Both networks have the same distribution of attributes, with 4 nodes in purple and 6 nodes in green. On the real network, we count 7 edges that share the same node color (same-to-same relationship) which are highlighted in red; while in the simulated network, we count 8. This result indicates that the real network has a bias towards nodes not sharing the same color because the simulation is assumed random and without bias. However, one simulation is not enough, and the result can be due to just random chance. Therefore, the process described on the right is repeated 1000 times, making a distribution of counted same-to-same simulated relationships.

This gives us a distribution of 1000 values from which we can extract a mean and a standard deviation. We then perform simple hypothesis testing, like a t-test, using the real amount of same-to-same relationships against a normal distribution given by the simulated mean and standard deviation.

We expand on this concept by instead of using the distribution of attributes in the general population of a node (i.e., *S. aureus* carrier prevalence being 30%), using the distribution of one specific category (i.e., *S. aureus* carrier prevalence in women being 20%) and repeating the same process for each category present in each attribute of interest (ie: women and men in sex, from underweight to obese in BMI, and so for). This gives us a new mean which then can be compared with the previous simulated distribution. In this way, we can check how much each of the categories deviates with respect to each other, and we can identify which category has a higher or lower risk for the outcome variable; if any.

Ideally, this technique should be done not by simulating similar networks, but by simulating every possible network and comparing those in which bias happens to those in which bias does not happen. However, it is impossible to find every possible network within reasonable computational time. So we need to reduce the number of possible networks based on some assumptions [149]. This allegedly gives the model properties that make it similar enough to all the possible networks. In our case, we use the same frequency tables with a network with the same topology as constriction. We also assume that the virulence of *S. aureus* would cluster carriers with carriers and vice-versa. As BMI homophily is high and the Chi-square table also suggests so, we also assume that this happens with subjects with similar BMI. Finally, we also assume that friends share similar environments and activities and this would be reflected in their vitamin D levels.

4.1.10 Friendship ratio

Biomarkers levels are a continuous variable and as such we cannot use the simulation approach unless we categorize them into something similar to "low level", "medium level", and "high level", losing some information in the process. Instead, we compare numerical levels between friends and non-friends biomarkers one by one. We do this by finding the ratio of, the average square difference between each person's biomarker level and friend's biomarker levels, and the average square difference between each person's biomarker levels and non-friends biomarker levels. Values significantly greater than 1 suggest that clusters of friends have similar biomarker levels in comparison with the rest

of the non-friend population, while values smaller than 1 would suggest the opposite. Values similar to 1 suggest nothing, however, we do not know a sensible threshold cut-off for this approach. We arbitrarily suggest that values greater than 1.1 or smaller than 0.9 are the significant ones.

4.2 Data cleaning

This section will present a summary of the important parts of the methodology followed in the data-cleaning process as well as the shortcomings encountered due to the experiment design or the original data-registering process. In the Appendix (chapter 7), some samples from the 25 tables with the original variables' names and a description of what each variable represents are provided, but we do not provide examples from tables that could potentially be used to identify students.

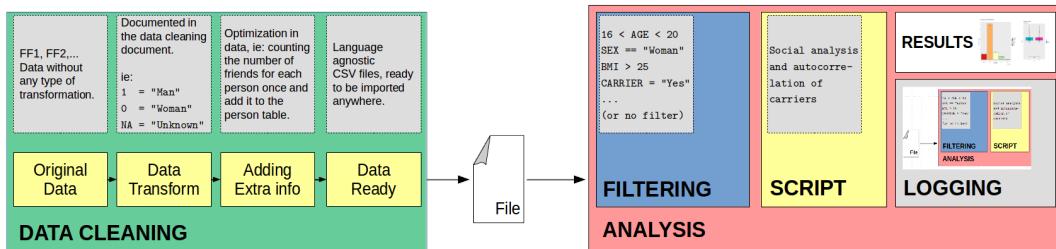


Figure 4.6: Overview of the data cleaning process. To the left, each step that transforms the raw data into a more practical version. This process is done only once. To the right, the subsequent analyses are performed as many times as needed.

Using our data will save time as it has been thoroughly cleaned, numerical data which is meant to be categorical has been given meaningful strings, diseases with just a verbal description with no code for International Statistical Classification of Diseases and Related Health Problems (ICD-10) has been assigned manually, and most importantly the data has been transformed into tables following proper Boyce-Codd normalization [150].

4.2.1 Naming

We changed their name to something more human-friendly and CSV and latex-compatible. This means using upper and lower cases appropriately, "ID" instead of "pers_key_ff1". Samples are labeled as S1 and S2 instead of the given FF11 or FF12 sub-time period. Direct culture and enrichment broth are simplified to "direct" (from STAPH in any case which is confusing) and "enrich". Units are included where possible in the variable name

("FE_FF1" to "Fe_(μmol/L)"). All FF id references are deleted as they are divided into Table_FF1, Table_FF2, and so on. Adding variable name continuity to quickly discern between binary and categorical variables ("FAT_FISH_FF1" to "FatFishFrequency") so the user already knows what to expect in each column. Deleting redundancy in names ("FRIEND2_CONTACT SCHOOL_FF1" to "Friend2School").

4.2.2 Dates

For all tables where a date appears, dates are standardized from several data formats (Posix, "mm/dd/YY", "dd/mm/YY", "YYYY-MM-DD") to "YYYY-MM-DD" format. Some of the dates could be transformed to have more precision down to "HH:mm:ss" resolution, but this information is irrelevant to us anyway so it is discarded. SPSS is the programming language that is used to encode the original data, and it uses the start of the Gregorian Calendar in 1582 as the default date for POSIX origin. Because of this chosen date reference, there might be some days' error in coercion in these dates because we do not know which timezone, or time origin, we take as a reference. We delete all timezones from UTC to simply a date, which we assume is GMT +1/+2 depending on the time of the year. Since the time difference is one to two hours, and we have a day resolution level, this loss of detail does not matter. It is advisable to use another non-SPSS method in the future as this time error coercion might render biological data which is time-critical unusable.

4.2.3 General tables

S.aureus

These tables contain the *S.aureus* information. Note that none of the FF11 variables are described in the metadata files. The information was retrieved from Fit Future experiment designers.

Swabbing information

All lab comments that are just registered as "OK" by lab technicians for all samples are discarded to avoid data redundancy. Also, all status and event variables are redundant information and are later discarded. All leading and trailing white spaces are deleted. None of these variables are described in the metadata and information.

What remains, for each unique nasal and throat swab, is whether the swabbing was performed successfully, with irregularities and the given reason, the swab was repeated,

or the swab was not performed at all. We also have the freezer ID of where to find each sample as well as the freezing date.

Blood serum and Blood Technical information

Several variables indicate if some value is above or below the healthy limit which are discarded. The reference on whether some value is healthy or not is marked during the analysis according to the given references for each value. Within the blood serum scope, there are also a bunch of columns named EVENT0 to EVENT9, and EVENTA to EVENTL, which are empty, no description is given in the metadata or any other source, and have no information at all. As such all of them are deleted. All LCMSMS (Mass spectrometry measures) have the same values as their normal measurements counterparts, so those are also skipped.

4.2.4 Relational Normalization

The original data does not have any type of relational meaning between columns. To add future benefits, we need to fix this issue due to privacy security [151], data logical consistency [151], and computational time efficiency. This section describes all tables related to relational data. The medicine, contraceptive, and disease tables are read from the original dataset and then transformed later into a structure that follows a proper relational database property.

The data should be organized in Boyce–Codd normal form [150]. Boyce-Codd normalization is important because it ensures that there are no data dependencies between columns, which translates into guaranteeing the integrity and consistency of data which is critical for accurate analysis. This is also crucial in datasets with large amounts of data, but this is not the case. Summarizing the normalization process, all variables and data in those tables need to be transformed so they follow these fundamental principles of normalization:

- **0NF** No information is lost and no information is duplicated.
- **1NF** No columns, or multicolumns (3NF), which contain sets of values.
- **2NF** Single column primary key (person ID) which is also used as superkey (4NF).
- **3NF** Eliminating the transitive functional dependencies.
- **BCNF** Always satisfies lossless join condition.

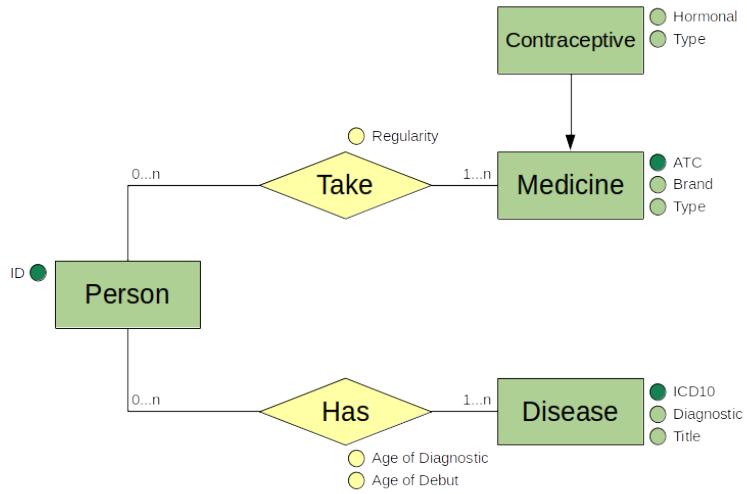


Figure 4.7: BCNF transformation from the original data. The database schema for "Person" can be obtained upon request.

4.2.5 IDs transformation

Each individual has a personal key described in the "pers_key_ff1" variable. The original key looks like this: "12345678" and is simply an 8-digit unique key for each of the 1038 individuals in that file. To avoid visual cluttering and math optimization, we substitute the original IDs with an integer number that goes from 1 to 1038, assigned randomly to each individual.

We have two special IDs. An ID equal to 0 means that a person has a friend that is not in our ID table, for example, it could be a student in another school that is not in Tromsø, or Balsfjord; in short, people who were not part of this study. An ID equal to -1 means no friend. This ID numbering keeps consistency later on when we do the filtering. This way, all the variables for each of the 5 friends have an integer, and is easier and faster to do math, indexing, and filtering. ID swapping log is registered in case identifying the original person is necessary but kept confidential.

4.2.6 Mapping

In this subsection, we discuss the relevant issues that arise during the mapping and transformation of the original variables. From the subsequent 29 tables generated during the mapping, we only provide a few relevant examples in this thesis.

S. aureus

Changes for Nasal and Throat variables are identical. This is also true for the variables for sample 1 and the variables for sample 2. In total, we have Nasal Sample 1, Nasal Sample 2, Throat Sample 1, and Throat Sample 2. Notice that all SPA-type variables remain the same.

School and education

Three columns represent "HighSchool", "Class", and "Programme". All of those have a numerical ID to represent the high school, a numerical ID to represent each class, and so on. While those can work ok the way they are, I choose to change them by adding a letter to each column to categorize it properly; these are not numerical values, these are categories. So high-school "1" becomes "H1", high-school "2" becomes "H2", class "10" becomes "C10", program "23" becomes "P23", and so for all values.

Sociology

Two variables expressed if "You live with 1 to 2 Siblings (yes/no/NA)", and "You live with 3 or more siblings (yes/no/NA)". Ideally, the questions should be: "How many siblings do you have? (number)", "How many siblings live with you? (number)". But we do not have that. However, we can convert those two variables into a single categorical variable that is expressed as "How many siblings live with you? (NA / Zero / One or Two / Three or more)". Regarding working status, the original data is also divided into too many variables that should not be, as they are sometimes mutually exclusive. The first one is "Is your mother studying?", "Is your mother a housewife?", and "Is your mother disabled?". All three of those are okay to have them separated as any combination of those (yes/no), plus working status, is possible. The rest of the possible answers refer to "Full time", "Part-time", "Unemployed", "Pensioned", "Deceased", "Don't Know", and "Other". All of those are grouped into the same variable within the same variable. Regarding ethnicity, the original question is not clear, and people have not answered ethnicity directly; instead, they have a combination of their country of origin, country of residence, country of parents, and their own race or cultural background. So here is the attempt to clear all that data into something useful. The final variable is a string with as many ethnicities as needed ("Norwegian", "Norwegian-Sami", "Belgium-Spain-France"). People who said they are Norwegian, Sami, or Kven, have a combined ethnicity if answered more than one of those, and also combined with whatever they write in the "Other" column where applicable.

We must express our concern that sharing the precise text from the "Other" category may lead to the identification of individuals. Researchers seeking access to the FF data can, however, apply for access to obtain the exact methodology.

Finally, we have these variables which are just a straightforward mapping "*Who do you live with? / What is your parents' educational background?*" In this case, while would be a fringe case, is possible to live with multiple combinations of these at the same time. For example, parents can be divorced while the student lives with both of them half of the time, each having a stepmother/stepfather, while the grandfather also lives inside one of the houses. So all of these variables are kept independent.

Puberty and Sleeping

These tables and serve as an example in which categorical data is overdone due to the string field limitations of SPSS/STATA data.

The variable for "At what age did your pubic hair start growing?" is, originally, saved as a categorical variable, that gets the values "1", "2", "3", "4", "5", "6", "7", that means from 9 to 15 years accordingly. This is changed from a categorical to a numerical value, however, the data is of course censored to the left and to the right since we do not have any other option. Ideally, we should have a real number instead of the category. For the rest of the men variables we have standardized all answers and eliminated references to the variable in each of the options, so instead of "Facial hair has not yet started growing", or "Voice has not yet started changing", both are mapped to "Haven't Started".

In table 4.4 we see that modeling a time of the day, into 18 different categories is not practical. A better solution would be, at the questionnaire level, to ask "At what time do you go to sleep?" so we can have a numerical value instead. This particular mapping is later transformed into "How many minutes since noon passes until sleeping time", which is a more sensible data format.

Table 4.4: Original values for the sleeping habits.

Variable	Original	Transformed
SleepingPills	1	Not used
	2	Less frequently than every week
	3	Every week, but not daily
	4	Daily
	NA	Didn't Answered
BedTimeHourCat	1	18:00 or earlier
	2	18:30
	3	19:00
	4	19:30
	5	20:00
	6	20:30
	7	21:00
	8	21:30
	9	22:00
	10	22:30
	11	23:00
	12	23:30
	13	00:00
	14	00:30
	15	01:00
	16	01:30
	17	02:00 or later
	NA	Didn't Answered

4.2.7 Diseases

All diseases are transformed into the proper relational table described earlier in section 4.2.4. There are plenty of transformations that need to be curated manually.

Common Diseases I

The questionnaire keeps track of diseases in three different ways. First, there are 7 diseases that the original data track explicitly, but do not register any ICD10 code. Those are "Diabetes" (unspecified which type), "Itchy Skin", "Hand Eczema", "Rhinitis", "Asthma", "Atopic Eczema" and "Psoriasis". The ICD10 codes can be seen in table 4.5.

Table 4.5: Table with the common 7 chronic diseases asked in a subsection of the questionnaire.

Questionary	Medical	ICD10	Comment
Diabetes	Other specified diabetes mellitus	E13	
Itchy Skin	Pruritus, unspecified	L29.9	
Hand Eczema	Dyshidrosis	L30.1	
Rhinitis	Allergic rhinitis, unspecified	J30.9	
Asthma	Asthma	J45.9	
Atopic Eczema	Atopic dermatitis, unspecified	L20.9	Skin and subcutaneous tissue
Psoriasis	Psoriasis, unspecified	L40.9	

Common Diseases II

The second way to track diseases is that during the interview, the student can tell up to 5 chronic diseases, and the ICD10 code is also registered by the person performing the interview. Again, in order to safeguard privacy, the initial response will not be displayed throughout this thesis. Instead, solely the conclusive compilation of ICD10 codes and their corresponding medical terms will be provided in table 4.6.

Table 4.6: Table with the up to 5 self-reported chronic diseases asked during the interview.

Medical	ICD10
Allergic rhinitis, unspecified	J30.9
ADHD	F90.9
Celiac disease	K90.0
Eczema	L30.9
Food allergy	T78.4
Migraine, unspecified	G43.909
Lactose intolerance	E73.9
Depression	F32.9
Anemia, unspecified	D64.9
Insomnia	F51.9
Diabetes Type 1	E10
Anxiety	F41.9
Tension headache (TTH)	G44.2
Gastritis	K29
Arthritis	M13.4
Hypothyroidism	E03
Asthma	J45.9
Eating Disorder	F50.9

It can be seen that some that were in the previous table are also repeated here. Redundant diseases are deleted. If the disease has more information (i.e.: "Diabetes

type 1" instead of "Diabetes"), we keep the most specific record. There are also some cases in which the person registered "Rhinitis" but assigned different "J30.X" codes to them. In this case, we changed the name "Rhinitis" to the ICD10 referred name. The disease "Migraine" is registered but no ICD10 was given, so we assigned the "G43.909" code.

Other Diseases

Finally, we need to look for all diseases that are written in the "Other" column. There is no further information here besides what the patient describes in one line of text, and no ICD10 code is given. People reporting two diseases at once are registered as two independent diseases. If the description here is more specific than in previous tables, then the information is updated. We have a total of 1133 instances of an individual linked to a disease, from which more than 10% came from cleaning this part of the data. We also have a total of 98 unique diseases, of which more than 75% come from this section alone.

4.2.8 Medicines

All medicine information, including contraceptives, is transformed into a proper normalization table as shown before. Is not described for all cases, but if possible, we include regularity information, meaning how often the person takes this medication. Notice that in the medicine table, we later also include the contraceptives that are hormonal in the list of medicines that this woman is taking.

There is one section of the interview where it is asked about regular medication. In the first one, detailed information is asked of the patient (i.e.: what is the name of the medication, the ATC code, and so on). There is also a section in the questionnaire where we have redundant information and it is only asked in a "yes/no" format (i.e.: "Have you taken sleeping pills in the last 4 weeks?"). In the second case, no regularity, no brand, and no ATC code are provided. We also have no information regarding whether this was a one-time-only event for this medication, if it was taken without a prescription, or any other extra information. Because of this, the second part is ignored since we cannot add a generic drug, or when specifically when it was consumed in the last 4 weeks. This affects the question regarding painkillers, sleeping pills, antidepressants, ADHD medication, and tranquilizers. People who take any of these regularly, have already filled this information in the first part of the questionnaire.

4.3 Ethical considerations

The Regional Committee for Research Ethics approved the Fit Futures study (REK North application ID 16773) and the analysis as part of the Tromsø Staph and Skin study - Fit Futures (REK North application ID 23432).

Chapter 5: Summary of main papers

5.1 Paper A

Social network analysis of *Staphylococcus aureus* carriage in a general youth population.

We explored the prevalence of *S. aureus* and risk factors in the FF1 population. Carriage prevalence was 30.4% for direct culture and 42.6% for enrichment broth. Both direct culture and enrichment broth showed a significant difference between males and females; with males having 36.4% and 48.1% prevalence, and females having 24% and 36.8% prevalence respectively. No other host factor was significant.

Students who attend the same high school tend to share the same Spa-type between them, which indicates that they share the same source of infection. The simulations indicated that school transmission is significant in the school network if the direct culture is used, and significant in the overall, physical, and school network if the enrichment culture is used. Simulation regarding Spa-type similarity indicated that transmission is relevant in all networks.

Males showed to have less connectivity than females, however, they have a higher prevalence. Autocorrelation regression also indicates that transmission happens in the network, but only the direct culture indicates that sex is a relevant factor. Our simulations indicate that sex and Physical Activity (PA) are relevant in both cases, which seems to indicate that women are at more risk of person-to-person transmission due to their higher connectivity. Autocorrelation also shows that Body mass index (BMI) and PA were relevant in both cases and the study program and alcohol for enrichment only. Our simulations indicate BMI and Alcohol for the direct culture only.

Finally, we estimated that a random student has an average increased risk of transmission of 3.5% with logistic regression, and an increased risk of 5% with auto-correlation, for each additional friend who is *S. aureus* carrier.

5.2 Paper B

"Friends are the sunshine of life" Social influence on vitamin D in a general youth arctic population.

Vitamin D is of special interest in the Arctic region; here we explored if friends tend to have similar levels. While vitamin D is not contagious from person to person, similar levels would indicate that friends share the same environment, activities, diets, or habits that promote or hinder vitamin D absorption.

First, we presented all possible factors that affect 25(OH)D levels in the blood. Diseases and medications were not relevant for this population. Then we checked which variables had a bias for each high school. This is because Ultraviolet B (UVB) influence overwhelmingly affects vitamin D absorption, and each high school had a different date for blood extraction across the year, differing traveling to sunny regions due to school calendar holidays, and different solarium habits. Without stratification, several levels are significant, but once the high schools are investigated one by one, only sex in H8, PA in H3, and holiday traveling in H1 and H3 were significant variables.

We also found out that women influence other women into going to the solarium, however, men do not influence other men. Currently, teenagers are banned from entering solariums in Norway due to their increased risk of skin lesions and cancer.

Among non-solarium goers, using logistic regression, we estimated that people with friends who have normal vitamin D levels ($>50 \text{ nmol/l}$) have a 7.25% chance of having normal vitamin D levels themselves for each additional normal vitamin D friend. We also checked this for high schools, and the influence was also significant among 5 of the 8 high schools.

Finally, we found contradictory results in the vitamin D levels concerning diet and vitamin D supplements. That is, people, eating fatty fish which is high in D3, or taking supplements that are extremely high in D3, do not show elevated levels of 25OHD in their blood. This is impossible. In the discussion part, we mentioned how different memory-based dietary assessment methods (M-BMs) can be used to improve the validity of dietary data, as well as Metabolic Equivalent of Task (MET) for PA.

5.3 Paper C

An introduction to network analysis for studies of medication use.

We presented how Network Analysis (NA) can help study medication usage regarding co-medications and drug interaction in the Norwegian population.

NA is underutilized in Drug Prescription Networks (DPN). As such we provided examples of how this type of analysis can help to analyze the relationships between prescriptions, health professionals, and patients. We accompanied this with a comprehensive tutorial on how to apply these methods using R and Stata syntax.

To accomplish this, we presented networks using the Norwegian Prescription Database (NorPD) in the elderly population, and another network of severe drug-drug interactions (DDIs) using the Norwegian Electronic Prescription Support System (FEST). In the results, we presented several statistics with their explanation for the reader to understand this type of analysis.

5.4 Result I

Social network influences on obesity in a general youth population.

We studied how friendship and social contact influence obesity. We saw that students tend to cluster together based on their BMI. Simulations indicate that students being friends with other students of the same BMI does not seem to be at random.

BMI increased almost $1\text{kg}/\text{m}^2$ on average from FF1 to FF2. We also show that students who belong to the "Healthy" group in FF1 have fewer chances of belonging to the same group in FF2 as their number of friends with $\text{BMI} > 25$ increases.

5.5 Result II

Social network influences on inflammatory response in a general youth population.

We found several results that suggest friends share similar inflammatory profiles among them.

A student's average biomarker level tends to be similar to his / her friend's average levels as well once sex and high school are accounted for. Similarities increase if we compare samples taken early in the academic year with samples taken later on. Furthermore, we introduced a distance metric which also suggests that friends have similar levels to non-friends.

We also tried to compare inflammation induced via social contact with inflammation resulting from obesity complications. Some biomarkers that correlated with anthropometric variables are not present in the social influence results; suggesting that the inflammation effect has a mix of both.

5.6 Result III

Measuring social influence with random forest regression and artificial neural networks.

We ran two machine learning models to predict FF2 BMI based on FF1 variables sex, BMI, smoking, snuff, alcohol, and sport frequency habits; as well as the number of underweight, healthy, overweight, and obese friends. We ran these models in 6 different subsets in which students increased, decreased, or stayed in the same BMI group from FF1 to FF2.

We used MDI and SHAP to measure the most important variables according to the ML models. After the initial BMI, in most cases, the total number of friends in each BMI group was evaluated as more important than the non-social variables.

5.7 Result IV

Frequency consumption of medication and social network influence in a general youth population.

We studied the possibility that students can influence each other's usage of over-the-counter medicines. These are often misused with unwanted side effects, or abused due to their potential as recreational drugs.

We saw a huge disproportion of reported diseases with respect to the reported medicines that are relevant for these diseases. In particular a spike in the use of anti-inflammatories and painkillers. Consumption by sex indicates that women tend to consume more of these medicines than men.

Hormonal contraceptives and painkillers seem to be associated with high schools. Anti-inflammatories and painkillers seem to be associated with sex. Simulations indicate that women who are friends share the same hormonal contraceptive brand.

Chapter 6: Discussion

6.1 Papers and results

6.1.1 Paper A

S. aureus transmission has been the subject of study on several occasions. Whether it is within the same household [152, 153], same hospital and ICUs [154, 155], or worldwide MRSA [156]. Also, social transmission of the beneficial or detrimental pathogen has been studied for HIV [157], and microbiota sharing among family and their pets [158].

To our knowledge, this is the first study to analyze social transmission in a general youth population. In 2023 another paper studied the spread of *S. aureus* in schools in England reaching similar results and conclusions to us [159].

We hypothesize that school is an important factor, not because the school itself is relevant, but because students spend more time together. However seasonal immunology is also a factor to be considered [160], and so far we have not been able to analyze this effect with confidence with only a one-time data point. For example, temperature, humidity, and vitamin D levels seem to drive the seasonal immunity for influenza [161]. It would be interesting to determine if a similar effect is relevant for *S. aureus*, especially considering that it is an opportunistic bacterium, adjusts a time series model accordingly, so the risk of transmission can also be adjusted depending on the time of the year.

Our results in **Result III** also show inflammation processes correlated as the academic year progresses and with schools individually. It is reasonable to think that infection risk increases in function over time, and so does the immune reaction that follows.

Defining what is a carrier of *S. aureus* is a difficult task in itself that took a considerable level of debate to resolve because we used two different growth methods. An alternative method to define a carrier or infected individual would be by using fuzzy logic. Fuzzy logic is a branch of mathematical logic that deals with reasoning and decision-

making in situations that involve uncertainty and imprecision. Classical logic operates on binary values (true/false), whether fuzzy logic allows for degrees of truth, in which logical propositions can be partially true or partially false. This approach has been used to improve chronic disease classification and decision-support systems [162, 163], and it would be interesting to see if it can perform well in graph models designed to predict disease spread in cases such as this in which a person can be a carrier of a bacterium, in different body tissues, at different enrichment levels of the sample, while also being asymptomatic.

6.1.2 Paper B

There are plenty of studies comparing ethnicity with vitamin D [164–170]. There is also at least one study comparing socioeconomic factors with vitamin D deficiency [171]. Although these variables tend to have a strong social component, to our knowledge no previous study has tried to study the social aspect of vitamin D. Other previous studies have measured the vitamin D prevalence in Tromsø [172–174], but again not the social aspect of it.

This paper is of particular interest in our Arctic population given how poorly vitamin D is absorbed via UVB radiation in this area. We can counter bad habits such as the described negative effect of solarium and recommend better activities such as PA so it has a spillover effect on the network. There are also plenty of external social influences regarding PA alone [175] which are not within the reach of this data and would be interesting to see and compare at the same time. Another nice follow-up would be how these recommendations would be effective in an adult and elderly population as their PA decreases while their traveling increases but as their capacity for vitamin D metabolism decreases with age as well [176].

One interesting approach from a public intervention point of view is that teenagers with no European background are especially vulnerable to vitamin D deficiency [177, 177–183]. In **Paper B** we discussed how immigrant populations tend to form strong community bonds. So public interventions targeted to this population to increase vitamin D levels would be quite effective.

Here we also discuss how future projects should gather data. There are plenty of improvements that can achieve better results with M-BMs and dietary data, and using MET for PA. Within the vitamin D topic, there are plenty of contradictory results [184–186] due to poor standardization or poor experiment design [181, 187, 188]. For

example, in our own data, we are not taking into consideration any interactions between foods [189, 189, 190]. It is paramount that we do not add confusion and noise to the literature; and that we start with proper data.

As previously commented, the immune system seems to be influenced as time passes by. Vitamin D promotes a homoeostatic effect on the immune system. If vitamin D is depleted over time, such as is the case in Tromsø where students come back from sunbathing in August and local UVB radiation is not high enough to fill them again, it would mean that unwanted type 2 immune reactions [191] are going to increase.

6.1.3 Paper C

Previous works have used network analysis to detect fraudulent opioid prescriptions [192] as well as being at risk of opioid abuse [193]. Another study from 2021 showed the capabilities of data mining using prescription networks in Italy [194]. Overall using SNA particularly to study prescriptions and find patterns has proven to be a useful tool for researchers and health professionals.

This paper, similarly to **Result III**, has been composed to demonstrate potential applications of a specific methodology. The results of DDIs are explored in other articles.

In our study, we saw that SNA can be useful in visualizing complex interactions and measuring clusters and central nodes with different metrics. Clusters in particular could be connected to pharmacological data to see the importance of pharmacokinetic interactions.

The bigger downside is to be able to draw the network in a meaningful way; not because this network is difficult to draw, but because plotting it is a general downside of SNA as we discussed during the background in section 3.2.4. Another downside to this network is that it is a bipartite network divided into prescriptions, patients, and medics. Bipartite networks are generally more complex to analyze. This makes the tool great for visualization and exploring but weak for hypothesis testing.

6.1.4 Result I

Here we saw that social dynamics behave in similar tendencies as in other teenage populations [195–199] where it is also shown that “*avoidance of overweight friends is the primary determinant of friendship patterns related to BMI.*” and “*a significantly*

greater proportion of obese/overweight versus non-overweight youth reported difficulty in making friends”.

A questionnaire on dietary habits, including vitamin supplementation, was given to the participants. However, our analysis of the dietary response, as shown in Paper B, shows that the self-reported diet habits are not a reliable answer, as the estimated nutritional intake from questionnaire data (selected food items with average frequencies of intake) does not correlate with the nutritional data retrieved from blood samples. As such, no nutritional data was included in this study so there is no assessment of how one person's diet influences another person's eating habits as well.

Another limitation of this study, which we try to partially overcome with Result III, is that we do not address how to move students from unhealthy BMI groups to healthy BMI groups. The second limitation is how to increase the connectivity from Healthy BMI to other groups as it would seem that groups tend to be self-biased and close to people from other groups.

6.1.5 Result II

There are plenty of papers that have explored the effects of inflammation and isolation [26], but to our knowledge, this is the first time that it has been studied how non-isolation influences other people's inflammation. This is important with IL-6 and C-reactive protein (CRP) in particular as they seem to be the leading factor in inflammation affecting loneliness. There also have been several studies linking biomarker levels with obesity. To name a few, ADA has been linked in mouse models with lower obesity and insulin resistance [200]. Axin-1 is correlated with glucose uptake in skeletal muscle [201]. BNGF has been linked with BMI and obesity regulation in a Scandinavian population [202]. Obesity-driven chemokine has been studied for CCL2, CCL13, CCL18-19, CCL23, CCL26, CXCL1, CXCL3 and CXCL14 [203]. Patients in the obesity group had higher IL-1beta, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-15, IL-17A, MCP-1/CCL2, MIP-1alpha/CCL3, MIP-1beta/CCL4, G-CSF, GM-CSF, FGF, IFN-gamma, and TNF-alpha than control group [204].

Here we see a positive correlation between IL-6, waist, hip, weight, and BMI in both men and women, plus a correlation between IL-6 within some high schools, and IL-6 being quite similar in between women's friends. IL-6 acts as a pro-inflammatory cytokine and as an anti-inflammatory myokine, it suppresses inflammation caused by stress in bones and muscles during exercise and promotes bone re-absorption. Myokines function is still

poorly understood but is believed to have a beneficial impact as a response to PA [205], which can be one of the reasons why women seem to have similar levels given that they do more PA than men in this population.

Another interesting result is that we can also see IL-10 and IL-13 correlating in women's friendships, and IL-10, IL-13, and IL-33 correlating with high school and sex. These are anti-inflammatory cytokines which would lead to believe social influence may alter the anti-inflammation profile of a student. Several chemokines related to immune hemostasis are also found across relevant results in both sexes, such as CCL 23, CCL 25, and CCL 28. In women's cluster of friends again, Brain-derived Neurotrophic factor (BDNF) is also associated with anti-inflammatory, chemotactic proteins that aid with diapedesis and extravasation of monocytes, and Macrophage colony-stimulating factor 1 (CSF1) it regulates osteoclast proliferation and differentiation and the regulation of bone resorption which might be interesting considering the sex differences of vitamin D levels seen in [Paper B](#).

A methodology shortcoming of this study is, as discussed previously in [Paper A](#), seasonal immunity effects are not taken into consideration. The study itself could be just a signal that we are measuring seasonality as each high school has different blood extraction dates and we are just seeing proteins reflecting immunity determined by time rather than high school influence.

For CRP, we found a very strong association for H6 women ($R^2 = 0.88$, $p-v < 0.001$), and a weak for H6 men ($R^2 = 0.22$, $p-v = 0.11$). Others Acute phase reactants (APR) would be interesting to study, in particular erythrocyte sedimentation rate (ESR) given that it takes way longer than CRP to return to normal levels after an inflammation process.

6.1.6 Result III

In previous studies [195,206] two strategies have been theorized regarding weight loss for overweight individuals. One that increases the total connectivity in general, and another one that increases the total healthy connectivity in particular. Obese students have low average connectivity, and they tend to be friends among themselves rather than with the general population. These results seem to indicate that the second strategy is better.

Initial BMI is the most important variable by far in all models. Individuals seeking weight changes should make necessary adjustments to their goals and refrain from relying

on methods that promise quick results.

In all models, after FF1 BMI, MDI evaluated healthy social contact influence in the final BMI more than any other non-social host factors including sport frequency. In general, SHAP evaluates some of the total friends' variables very highly alongside sex and sports frequency. General high connectivity with healthy friends seems to be a good contributor to lower BMI or to prevent further BMI increase. General high connectivity with overweight friends seems to be a bad contributor to increasing BMI or preventing further BMI losses. Only group D seems to have a negative correlation, but the effect is small (-0.15 BMI from 0 to 3 overweight friends).

These results follow the previous analysis done in [Result I](#) where we see that FF2 BMI is proportional with connectivity with high BMI individuals. We also observed that students have a bias toward choosing friends of the same BMI category. How to break this bias is beyond the scope of this study, but social relationships seem to be as important as doing sports in aiding overweight and obese individuals to lose weight.

It would be interesting to figure out why Healthy students stopped being healthy and advanced to an Overweight or worse state. But model E seems hard to interpret by our model. Further data regarding if these people change their habits with time (i.e.: Sport was "hard" in FF1 but then "none" in FF2 two years later) would be useful.

Sports are evaluated as having high importance by MDI and SHAP to stay Healthy but seem to be of not much relevance when you increase or decrease your weight. Sports are generally also evaluated as a strong variable indicator. Sports increase the metabolism and total energy consumption, but if the energy intake is still greater than the energy spent in sports, then weight loss is not possible. In this dataset, we do not have a healthy diet adherence evaluation, as it could be for example the 14-Item Mediterranean Diet Adherence Screener (MEDAS). Further analysis that includes food questionnaires is needed to evaluate how diet is influenced by social contacts, and how important it is with respect the social influences.

In these results, we used some naive approaches to building machine learning models and used a limited set of explainability techniques. Our main goal was to show that this is useful and the results are important, rather than fine-tuning each model accordingly for each dataset; which in particular is self-evident with dataset E.

6.1.7 Result IV

Other works have presented the over-the-counter usage in Norway [118], and have also been speculated, such as "*Parents' symptom experience seems to influence their children's medicine use over and above medicine use indicated by symptoms. Two potential explanations are suggested: a socialization pathway and/or a pathway through adverse living conditions.*" [207], which links medicine abuse to the social network influence. Once again, to our knowledge, no other article has analyzed the social aspect.

In Paper C we discussed how other works detected substance abuse using SNA. Here something similar is achieved in specific high schools showing a disproportionate amount of medicines with respect to diseases, and how social influence affects this.

Painkiller usage is biased within high schools. This should not happen under normal circumstances, as both the diseases related to pain, and the use of over-the-counter drugs should be spread across high schools randomly. Pain-related diseases are indeed spread fairly balanced across high schools, but not the medicine part. The use of anti-inflammatory bias in women can be explained by the use of medication during menstrual cramps. We can see that the use of Naproxen (brand name Naprocyn) is 100% females as this is an NSAID mainly used to treat such pains.

The main concern of these results is whether students are using painkillers as recreational drugs, the same as seen in other populations [208]. While these results should raise some attention, are not direct proof of anything. A proper follow-up questionnaire should be addressed and asked directly "*Have you ever used over-the-counter medicine/self-medication with non-medical purposes? If so, in which period of time and what frequency?*".

Previous work studied the relationship between pain threshold and friends' influence and inflammation response [209]. The bias that we saw in painkiller consumption at the high school level might be partially explained due to some high schools having lower pain resistance in general. However, we do not have access to the pain threshold data to investigate this approach further.

This data is also from the 2010s, being not a well-up-to-date reflection of current teenage drug activities. For example, in recent years "U-47700" has been popularized as a Non-Fentanyl Synthetic Opioids [210] and it could be that current teenagers are ditching painkillers for this drug, or any other alternative.

6.2 Direct influence vs common environment

From here, I will now proceed to address the overarching themes within the thesis.

Two influences can be detected using social network analysis. The first one is the influence that is shared directly by contact, such as in the case of **Paper A**, where bacteria jump from person to person. The other way is by sharing the same environment as with **Result II**; the inflammation process cannot jump from person to person but they both can share an environment in which allergens, and irritants, or toxic compounds are present, which can lead to common inflammation reactions. Realistically, in most cases, we will have a bit of both cases all the time. In **Result II** we can also have a shared microbe going around the schools. In **Paper B** students share an environment with the same amount of UVB, and even though we were not able to measure it, it is likely that they share a similar diet and PA.

A significant limitation of social network analysis is that this method is unable to tell if direct influence or common environment or both are happening and needs the support of other classical statistical methods or direct measurements, to be able to tell which are the reasons why people have common levels of something. For example, in **Result II** we see that people belonging to the same school share inflammation processes as the school year progresses.

However, a significant advantage, is that social analysis can be done very quickly. It is unrealistic to expect constant monitoring of allergens, diets, pathogens, and so on in every environment in the population. But we can monitor and detect trends in people's health immediately. This might lead to us being able to tell that friends in a particular environment (school) are getting unhealthy levels or whatever concept we are interested in. If we were to only measure the general population instead of grouping by friends we could lose significant patterns as we show in **Result II**, in which analyses stratifying by sex only shows no significant results; even though the effects are already there. This could lead to being too late to do something of value to stop the health hazard in time.

6.3 Optimization of resources in public interventions

In the introduction (section 1.2) examples of how SNA optimized public health interventions and resources with little cost were presented. This is something that we would like to validate further with our results.

For example, in **Paper B** we see that women influence other women into going to the solarium, but men do not influence other men. Solariums are a horrible idea that leads to a significant increase in skin cancer lesions with insubstantial benefits [211]. As such we would like to convince the population to stop going to the solarium. Based on our results, an optimal approach would be to target women in an ad campaign rather than the general population. We see something similar in **Paper A** in which men are more common carriers of *S. aureus*, but women are more at risk due to social contact. In **Result III** we associated an increased risk of obesity due to social contact with overweight friends, and a lower risk with healthy-weight friends, so a better approach would be to increase network connectivity between these two groups. **Result IV** shows which high schools tend to have biased use towards painkillers, so we can concentrate efforts on drug prevention campaigns there.

A second important concept is the spillover effect [212–215] which is discussed in **Paper B**. In a network, especially one with a hierarchical topology, it is possible to target the top hierarchical behavior which would make the hanging nodes copy this behavior propagating the health effects throughout the network, instead of targeting all nodes at the same time which takes time and efforts which we might not be able to afford. This is similar to any marketing campaign in which internet influencers (top nodes) are paid to promote a product among the followers (hanging nodes).

6.4 Challenges in privacy

We encountered some data points that potentially allow for the identification of individual students. This exemplifies why the use of the Boyce - Codd normal form (BCNF), described in methodology (section 4.2.4), is important, as it mathematically guarantees that access to information contained in tables that a person shouldn't have access are kept in those tables and not outside of it.

These events are reported back to the head of the appropriate department and corrected. In a future manuscript, we will list all the "lessons learned" from the data cleaning process and help to develop better protocols for future epidemiology studies.

6.5 Challenges in reproducibility

In science, you have not discovered something until you discover it and somebody else reproduces it. All our code is open source (Afferro GPL3.0 [216]), however, due to

regulations in Norwegian law [217] and privacy ethics [218], the data is only available upon request. For example, a legal limitation is that subjects under 16 years old must sign special consent which includes limitation to the data access. This can limit the ability of other researchers to replicate and validate the results of our studies, which can lead to a lack of confidence in the findings. This also hinders the ability to build upon our methods. Any push to allow for more flexible data access can also hinder the trust of the public who gave us the data in the first place, hindering in this case any future project.

This is a very serious limitation that we need to overcome, and luckily there is one particular example that can be used to inspire future projects. There's however another project, the Tromsø Study [219], which has a more flexible approach. For example, all the metadata is [open and publicly available](#), including some basic descriptive statistics for many of the variables.

Despite the similarities between the two cases, data remains accessible only upon request. In the future, it would be beneficial to adopt a more open approach to data collection while ensuring the public's trust is maintained. In 2017, a systematic review found only one study discussing how data could be more open: *"this systematic review of the literature has uncovered a lack of evidence-based incentives for researchers to share data, which is ironic in an evidence-based world"* [220] Another similar study of 2020 [221], highlights the paradox of how open data is widely supported by researchers, publishers, governmental institutions, and is even a necessary condition for asking for funding; and yet the sharing of the data is heavily restricted due to publication pressure and fear for competition.

6.6 Challenges in framework developing

We have successfully developed a framework that automatizes most of the tedious scripting aspects. However, we found that R was quite limited in comparison with other programming languages [222]. As such, we are putting our effort into developing this framework into other languages in the future which would be less complicated than trying to keep updating and maintaining our current packages.

When it comes to performance, large-scaling computing is not an option in R, especially since R does not have built-in support for multithreading. While techniques such as the use of RCPP library [223] can integrate C++ into R, is just an unnecessary mid-

dleman. On top of this, R and the de-facto Integrated Development Environment (IDE) RStudio, have limited memory management capabilities, which can lead to memory leaks and slow down the performance of R scripts even further.

While performance is a deal breaker in the long run, this does not affect our data too much since we barely have about 1000x1000 tabular matrices which is not much. However, what pushes us to abandon further support for the future is the lack of proper object-oriented programming and lack of standardization. R does not have strong support for object-oriented programming. R aimed to retain the core functionalities and syntax of S while adding modern features and extending its capabilities. However, S was designed as a language for data analysis and a graphical representation [224], primarily used for statistical modeling and visualization which back in the 1970s did not have in mind the very strong paradigms of object-oriented programming that C++ would properly develop years later during the 1980s. As a result, R was developed in the 1990s, trying to use the 1970s syntax, but somewhat trying to appeal to modern functionality. Even though R does not have to deal with pointers, and memory management like in C++, R has a steeper learning curve than Python or C++ in the long run due to its lack of core personality. Making Python a much better option for beginners a C++ a better option for software professionals. In both cases, all the statistical-related functionality that R specializes in is also available in both of these languages.

From our own experience, R sometimes might appear difficult to work for people who know other programming languages like computer science professionals, but loved by people who are used to working with SPSS or Stata. We tried to satisfy this last group, but now the limitations have become clear, and we should be pushing scripting and programming to be done in Python or C/C++ as in both cases, in the long run, will produce better scripts and final products with much less hassle.

6.7 Future projects

Several small-molecule inhibitors and monoclonal antibodies against Fibronectin binding protein A (FnBPA) [225, 226] are being tested in intrahospital environments [227]. All the social influence techniques we have discussed and presented so far, especially those related to *S. aureus* hospital-acquired infections [155, 228], can be applied to study nosocomial infections related to *S. aureus* to show the effectiveness of preventing transmission using these inhibitors.

SPMs is highly associated with a fish-rich diet. Friends tend to have similar diets, so the similar good inflammatory process might be due to sharing similar pro-inflammatory or anti-inflammatory diets. As discussed in Paper B , we need to refine the dietary data in FF or use another dataset, before we try this approach.

A forthcoming manuscript uses lessons learned in this thesis regarding FF for future epidemiological studies. This is of high interest because future epidemiological studies need to optimize the organization of the data better to minimize the work described in section 4.2, which is currently repeated over and over by different researchers. Other practices while analyzing the data need to be revised as well.

We had very limited access to the FF2 dataset, which did not include the social network. We also did not get any data from FF3. There are plenty of studies that can be done using longitudinal data between FF1, FF2, and FF3. For example, on the topic of how is health affected at a later age by a person's social network as the year progresses?; how does *S. aureus* colonization evolve as the social network changes? , does inflammation markers change when we get new friends? does over-the-counter misuse get better or worse over time?

We have a very limited dataset from FF2, which is unrelated to the social network, and no data from FF3. There are plenty of studies that can be done using longitudinal data; mostly on the topic of how health is affected at a later age by the social network as the year progresses.

Chapter 7: Conclusions

This document showed the multiple applications that SNA have in our population within a broad range of topics. In Paper A we saw how *S. aureus* transmission is more associated with women's social interactions and how schools have distinctive strains measured by their Spa-typing. Result II also showed the importance of school interaction concerning immune response and inflammation as the academic year progresses. Result I and Result III showed the importance of friends in the quest for a healthy BMI. Paper B shows solarium influence in women and underlying influences related to social contacts about vitamin D levels. Result IV also hints at how hormonal contraceptive usage is shared among communities and some concerning usage of OTC medicine shared in schools.

We showed the application of non-parametric simulations and machine learning methods in studying social influences. We developed an easy-to-use framework in R and showed easy-to-use examples in Paper C, but due to several drawbacks, mainly maintenance of big libraries, is going to be ditched in favor of the Python and C++ implementations in the future.

We show several metrics to quantify these influences. However further work and discussion with health professionals are needed to determine the best way to impact policy-making based on these results at a lower cost.

In summary, this thesis provides evidence that suggests social influence is currently present in many topics, and accounting for this factor is as important, if not more, than accounting for other classical variables such as smoking or PA. We have also sadly experienced recently the necessity to account for social interactions during the SARS-CoV-2 pandemic, which also demonstrated a good example of why this type of analysis can be critical.

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Appendix A: Main papers

A.1 Paper A



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Social network analysis of *Staphylococcus aureus* carriage in a general youth population



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ABSTRACT

Objectives: *Staphylococcus aureus* carriage increases the risk of infection. We used social network analysis to evaluate whether contacts have the same *S. aureus* genotype indicating direct transmission or whether contagiousness is an indirect effect of contacts sharing the same lifestyle or characteristics.

Methods: The Fit Futures 1 study collected data on social contact among 1038 high school students. *S. aureus* carriage was determined from two nasal swab cultures and the genotype was determined by spa-typing of positive throat swabs.

Results: *S. aureus* carriage and spa-type were transmitted in the social network ($P < 0.001$). The probability of carriage increased by 5% for each *S. aureus* positive contact. Male sex was associated with a 15% lower risk of transmission compared to the female sex, although the carriage prevalence was higher for men (36% vs 24%). Students with medium physical activity levels, medium/high alcohol use, or normal weight had a higher number of contacts and an increased risk of transmission ($P < 0.002$).

Conclusion: We demonstrated the direct social transmission of *S. aureus*. Lifestyle factors are associated with the risk of transmission, suggesting the effects of indirect social groups on *S. aureus* carriage, such as friends having more similar environmental exposures. The male predominance in the carriage is determined by sex-specific predisposing host characteristics as the social transmission is less frequent in males than females. Information on social networks may add to a better understanding of *S. aureus* epidemiology.

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Introduction

Nasal carriage of *Staphylococcus aureus* has a prevalence of 20–30% in the general adult population (Olsen *et al.*, 2012; Stensen *et al.*, 2021)

and 40–50% in older children and adolescents (Stensen *et al.*, 2019) and is more common among men than women (Olsen *et al.*, 2012). Carriers have an increased risk of autoinfection (Bode *et al.*, 2010; Wertheim *et al.*, 2005). Therefore, prevention of nasal carriage may reduce the disease burden of *S. aureus* (Bode *et al.*, 2010). Epidemiologic studies have searched for modifiable risk factors for *S. aureus* nasal carriage as potential targets for interventions, including body mass index (BMI), serum glucose and vitamin D, exogenous and endogenous hormones, and smoking (Johannessen *et al.*, 2012; Olsen *et al.*, 2012; Olsen *et al.*, 2013;

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[Sangvik et al., 2011](#); [Stensen et al., 2019](#); [Wertheim et al., 2005](#)). However, these studies did not adjust for social contact.

Direct transmission of *S. aureus* is primarily through physical contact ([Knox et al., 2015](#)); however, no other study has evaluated the direct social transmission of *S. aureus* carriage in young populations. In studies that involve transmissible pathogens, an extensive problem with identifying the risk factors is the lack of adjustment for social contact. Biological host risk factors for *S. aureus* carriage may also be determinants of friendship, thereby producing an association by confounding. Predisposing lifestyle risk factors may be contagious with the consequence of researchers incorrectly assuming the transmission of the pathogen. Prevention of *S. aureus* carriage is dependent on identifying key transmission pathways and causal risk factors to correctly evaluate targets for interventions.

Infectious diseases like tuberculosis, HIV infection, and sexually transmitted diseases have been strongly connected to social networks ([Jolly and Wylie, 2002](#); [Klovadala et al., 2001](#); [Rothenberg et al., 1998](#)). These studies demonstrate that the degree and type of contact between individuals play a significant role in disease incidence. One study showed that the introduction of *S. aureus* into a social network of active drug users created a reservoir for the bacteria linked to the general population ([Gwizdala et al., 2011](#)). A recent case-control study used network analysis to reveal the transmission of methicillin-resistant *S. aureus* (MRSA) through social network in healthcare ([Moldovan et al., 2019](#)). Social group effects also occur in humans, as unrelated individuals living in the same household are found to have more similar microbiota than relatives living in different households ([Song et al., 2013](#)). Transmission of *S. aureus* has also been observed within households ([Miller et al., 2009](#)).

Therefore, the aim of this study is to estimate the extent to which *S. aureus* carriage follows friendship ties and whether the data support the concept of direct social transmission. We also aim to identify host risk factors for *S. aureus* carriage and differentiate between the risk attributable to social contact among similar individuals compared to biologic or lifestyle-related risk.

Methods

Population and study design

The Fit Futures 1 study (FF1) was a youth health survey conducted from September 2010 to April 2011, inviting all first-year students registered at 8 high schools in the municipalities of Tromsø and Balsfjord, North Norway. Altogether, 508 female and 530 male students participated in the survey (93% participation) ([Winther et al., 2014](#)). Participants visited the Clinical Research Unit of the University Hospital of North Norway (UNN) for interviews, questionnaires, clinical examinations, and microbiological samples. Trained research nurses performed all the procedures according to a standard protocol.

Host risk factors

Participants wore light clothing and no shoes. Height (cm) and weight (kg) were measured on an electronic scale with participants wearing light clothing and no shoes, and BMI (kg/m^2) was calculated. The participants reported their sex, age, study program, tobacco use, alcohol use, and recreational physical activity through a web-based questionnaire.

The interview covered current hormonal contraceptive use. We categorized hormonal contraceptive use into progestin-only contraceptives and combination contraceptives with high or low ethinylestradiol dosage ([Stensen et al., 2019](#)).

Assessment of *S. aureus* carriage

The research nurses took a first set of nasal and throat swab samples at the hospital, and a second set at school after a mean interval of 17 days. Nasal vestibules were sampled using the same 0.9 % NaCl-moistened sterile rayon-tipped swab, and both tonsillar regions were sampled with another swab. The swabs were immediately placed in a transport medium (Amies Copan, Brescia, Italy) and stored at 4°C for a maximum of 3 days. All samples were analyzed at the Department of Microbiology and Infection Control, UNN, both by direct culture ([Olsen et al., 2012](#)) and enrichment culture ([Stensen et al., 2019](#)) (Bacto Staphylococcus medium broth, Difco Laboratories, Sparks, Maryland, USA), using blood agar for growth control (Oxoid, UK) and chromID-plates for *S. aureus* detection (SAID, bioMérieux, Marcy l'Etoile, France) and MRSA agar plates SmithMed AS/Microbiological media production, Department of Microbiology and Infection Control, UNN). The growth of any bacterial colonies on agar plates was registered as a valid sample. The dominating *S. aureus* colony type was frozen at -70°C in glycerol-containing liquid medium after confirmation by Staphaurex plus agglutination test (bioMérieux, Marcy l'Etoile, France).

We used *S. aureus* persistent nasal carriage as the main outcome variable in the present analysis as this has been the major phenotype of interest in infection control and epidemiologic studies ([van Belkum et al., 2009](#)). We defined persistent carriage as having either two positive direct cultures or two positive enrichment cultures (Supplementary Figure 1). All *S. aureus* isolates from the first throat swab sample taken at the hospital were spa-typed (staphylococcal protein A) as part of another study by [Sangvik et al. \(2011\)](#).

Social network

We constructed the social network based on the interview question: "Which first level high school students have you had most contact with the last week? Name up to five students at your own school or other schools in Tromsø and Balsfjord." Reciprocity in the nomination was not mandatory. For each nomination, five "yes/no" questions assessed the type of contact: "Did you have physical contact?", "Have you been together at school?", "Have you been together at sports?", "Have you been together at home?", "Have you been together at other places?". This gave five social networks depending on the setting: "physical contact", "school", "sport", "home", and "other" networks. Adding all the relationships together formed a sixth network that was called the "overall" network. To evaluate if the friends mentioned were representative for the participants' social network, the following question was asked: "To what degree does this list of friends give an overview of your social network? Please indicate on a scale from zero (small degree) to ten (high degree)." We excluded 134 nominated friends that did not participate in FF1.

Statistical analysis

We used R version 3.6.3 and R Studio 1.3.1093 for the statistical analysis. To evaluate univariable associations between host factors and *S. aureus* persistent carriage we used Student's *t*-test and chi-square test, with Yates's correction for 2 × 2 tables and Fisher's exact test, when applicable.

In the social network analysis, nodes refer to participants in the network while edges refer to lines representing relationships between participants. To evaluate transmission of *S. aureus* through the social network, we analyzed edges between nodes using Exponential Random Graph Models or additive and multiplicative effects models. We analyzed patterns of connections (non-carriers

Table 1

Characteristics of the study population by *Staphylococcus aureus* persistent nasal carriage determined by direct and enrichment culture. The Fit Futures 1 study (N = 1038).

	Direct culture			Enrichment culture		
	Positive ^c	Negative ^c	Prevalence	Positive ^c	Negative ^c	Prevalence
Sex	< 0.001			< 0.001		
Male	193	337	36.4 %	255	275	48.1 %
Female	122	386	24.0 %	187	321	36.8 %
Study program	0.99			0.08		
General	118	272	30.3 %	163	227	41.8 %
Sports	31	73	29.8 %	55	49	52.9 %
Vocational	166	378	30.5 %	224	320	41.2 %
Smoking	0.93			0.48		
Daily	14	34	29.2 %	24	24	50.0 %
Sometimes	59	129	31.4 %	76	112	40.4 %
Never	236	546	30.2 %	333	449	42.6 %
Snuff use	0.79			0.30		
Daily	73	172	29.8 %	107	138	43.7 %
Sometimes	43	88	32.8 %	63	68	48.1 %
Never	192	450	29.9 %	263	379	41.0 %
Body mass index category	0.21			0.22		
< 18.5 kg/m ²	35	75	31.8 %	55	55	50.0 %
18.5–<25 kg/m ²	201	509	28.3 %	289	421	40.7 %
25–<30 kg/m ²	54	93	36.7 %	68	79	46.3 %
≥30 kg/m ²	22	45	32.8 %	27	40	40.3 %
Physical activity^a	0.15			0.07		
None	80	149	34.9 %	107	122	46.7 %
Light	99	239	29.3 %	129	209	38.2 %
Medium	67	192	25.9 %	105	154	40.5 %
Hard	63	131	32.5 %	93	101	47.9 %
Alcohol intake	0.32			0.780		
Never	88	192	31.4 %	115	165	41.1 %
≤ 1 Month	134	286	31.9 %	183	237	43.6 %
≥ 2 Month	86	232	27.0 %	134	184	42.1 %
Hormonal contraceptives^b	0.76			0.68		
Non-user	78	249	23.9 %	121	206	37.2 %
Progestin-only	3	17	15.0 %	5	15	25.0 %
Combination contraceptives, low estradiol	12	38	24.0 %	19	31	38.0 %
Combination contraceptives, high estradiol	26	73	27.1 %	39	60	39.4 %

^a Physical activity in leisure time: None = reading, watching TV, or other sedentary activity; Low level = walking, cycling, or other forms of exercise at least 4 hours a week; Medium level = participation in recreational sports, heavy outdoor activities with minimum duration of 4 hours a week; High level = Participation in heavy training or sports competitions regularly several times a week.

^b Hormonal contraceptives: Non-user = No current use of hormonal contraceptives (women only); Progestin-only = Use of hormonal contraceptives with progestin (Cerazette, Neplanon, Depo-provera, Implanon); Combination contraceptives, low estradiol = Use of hormonal contraceptives with progestin and ethinyl estradiol less than or equal to 20 µg (Mercilon, Yasminelle, Loette 28, Nuvaring). Combination contraceptives, high estradiol = Use of hormonal contraceptives with progestin and ethinyl estradiol greater than or equal to 30 µg (Marvelon, Yasmin, Microgynon, Oralcon, Diane, Synfase, Evra, Zyrona). Women taking contraceptives, but who were unable to recognize the brand were removed from the analysis.

^c Positive = two consecutive nasal swab cultures positive for *S. aureus* Negative = one or none of two consecutive nasal swab cultures positive for *S. aureus*.

connected to non-carriers, non-carriers connected to carriers, carriers connected to carriers) using the autocorrelation model Simulation Investigation for Empirical Network Analysis (O'Malley and Marsden, 2008). In further analysis, we used bootstrapping of simulated networks against the observed network, descriptive analysis, and logistic regression to evaluate the effect of host risk factors. The statistical background for our methods is described in Supplementary material.

Results

Transmission of *S. aureus* carriage in a general population

In the general population with a mean age of 16.4 years (SD = 1.24, range 15–28), the prevalence of *S. aureus* persistent nasal carriage determined by direct culture was 30.3%, compared with 42.6% when using enrichment culture. No MRSA isolates were detected. Prevalence of persistent carriage was higher in male

compared to female participants; 36.4% versus 24.0% for direct culture, and 48.1% versus 36.8% for enrichment culture. We found no other significant differences in carrier prevalence between groups according to host characteristics (Table 1).

We first evaluated the FF1 social network structure based on all relationships between students in the five subnetworks (Supplementary Figure 2) and information about relationships and persistent carriage status of nodes in the "overall" network diagram (Figure 1). As the population was recruited from two neighboring municipalities, there were two distinct clusters of students. The number of edges within the high school cluster was higher than outside the cluster demonstrating high school as a strong driver of friendship (homophily of 87.8) (Figure 2). Likewise, participants tended to bond with similar students with respect to sex and lifestyle factors (Supplementary Table 1 and Supplementary Figure 3).

To evaluate the effect of the social network on transmission, we assessed relationships that shared the same *S. aureus* spa-type in

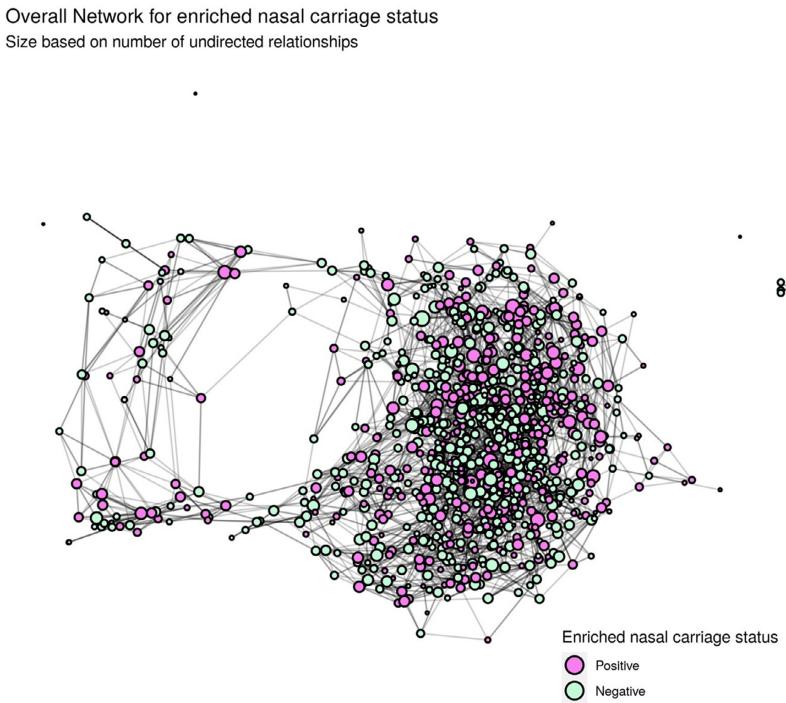


Figure 1. Overall network. The Fit Futures 1 study (N = 1038). *Staphylococcus aureus* persistent nasal carriage status determined by enrichment culture is highlighted for each student (Positive = *S. aureus* detected in two nasal swab samples; Negative = *S. aureus* detected in one or none of two nasal swab samples). Node size is proportional to the number of connections (undirected friendship).

the “overall” network. We registered 212 unique spa types among *S. aureus* throat isolates from 746 students. The 15 most prevalent spa types are listed in Table 2. The network analysis demonstrates that each high school has a unique distribution of spa types. Overall 126 edges of *S. aureus* carriers shared the same spa type. A total of 105 edges (83.3%) connected within the same high school, while 21 edges (16.7%) connected across different high schools (Figure 3). This suggests that spa-type is associated with friendship. The inclusion of non-typeable *S. aureus* strains did not affect the results and was therefore excluded from the analysis.

To test if there was a statistically significant influence of social networks on the transmission of *S. aureus*, we performed simulations of the current population for the six networks (Table 3). In the “overall” network, the transmission of *S. aureus* could be demonstrated for the persistent carriage determined by enrichment culture ($P = 0.02$). Transmission could also be demonstrated in the “school” network (direct culture: $P = 0.02$; enrichment culture: $P = 0.01$) and in the “physical contact” network (direct culture: $P = 0.06$; enrichment culture: $P = 0.04$). The same simulation-based analysis for spa-types showed transmission of *S. aureus* genotypes in all six social networks ($P < 0.001$).

The role of host risk factors in *S. aureus* transmission

In the logistic regression analysis, female participants had the highest risk of being exposed to *S. aureus* through their social interaction (Table 4). Men had a relatively low risk of transmission compared to women (0.85, 95% CI = 0.805–0.884). Also, students using alcohol twice or more per month had a higher risk of transmission of *S. aureus* compared to students using alcohol once per month or less ($P = 0.035$; direct culture). There was a higher probability of transmission among participants doing medium-level physical activity ($P = 0.008$) compared with the light physical activity group.

The mean number of friends for female students was 3.46, which was significantly higher than the average of 3.46 friends among male students ($P = 0.008$) (Supplementary Table 3). Students consuming alcohol more than twice a month had a higher number of friends compared to those consuming less or no alcohol ($P < 0.001$).

We demonstrate that students with a higher number of friends being persistent carriers were more likely to be persistent carriers themselves. This was significant for persistent carriage defined

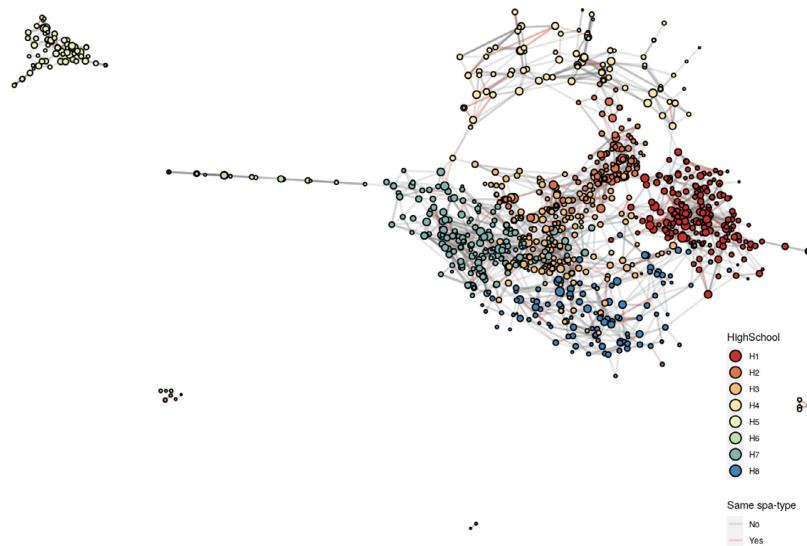


Figure 2. The overall social network within and between high schools, with a multidimensional scaling layout. The Fit Futures 1 study. Edges (lines) connecting nodes (students) with the same *Staphylococcus aureus* spa-type in throat culture are drawn in red. Edges connecting nodes with different spa-type are drawn in gray. High school ID (H1-H8) represents the eight high schools included in Fit Futures 1. H5 represents students at the high school in Balsfjord municipality (isolated cluster, upper left). All other high schools (H1-H4, H6-H8) are in Tromsø municipality. Only students with *S. aureus* isolated by direct or enrichment culture from the first throat swab sample are shown ($N = 746$). Unconnected students are not included ($N = 21$).

Table 2

The most prevalent spa-types for *Staphylococcus aureus* throat carriage. The Fit Futures 1 study ($N = 746$). Only persistent carriers are shown. The plots are the results for enrichment culture.

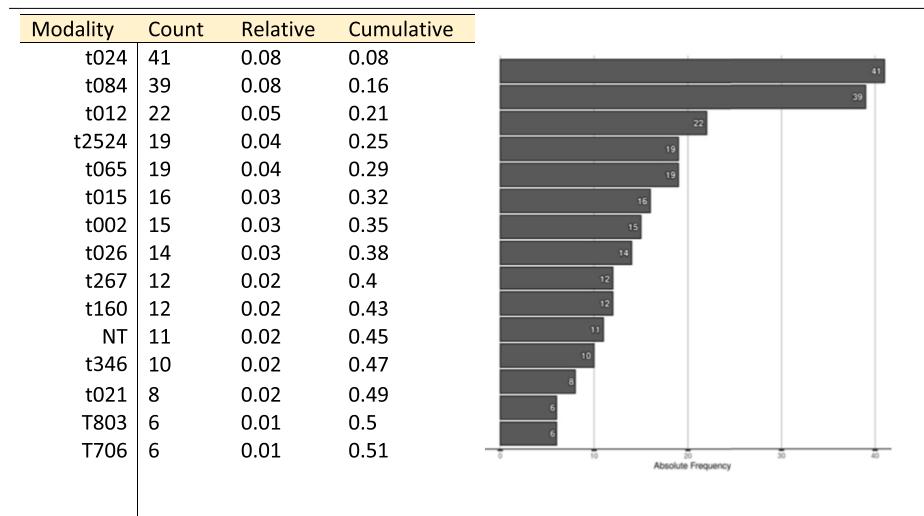




Figure 3. The overall social network with students grouped by high school. The Fit Futures 1 study. Edges (lines) connecting nodes (students) with the same *Staphylococcus aureus* spa-type in throat culture are drawn in red. Edges connecting nodes with different spa types are hidden. High school ID (H1-H8) represents the eight high schools included in the Tromsø Study Fit Futures 1. H5 represents students at the high school in Balsfjord municipality. All other high schools (H1-H4, H6-H8) are in Tromsø municipality. Only students with *S. aureus* isolated by direct or enrichment culture from the first throat swab sample are shown ($N = 746$). Unconnected students are not included ($N = 21$).

Table 3
Summary of 1000 simulations for each type of social network with respect to *Staphylococcus aureus* persistent nasal carriage and *S. aureus* spa-type. The Fit Futures 1 study. A detailed summary of this analysis is presented in Supplementary Table 4.

Network	<i>S. aureus</i> persistent nasal carriage		<i>S. aureus</i> throat colonization
	Direct culture ($N = 1038$)	Enrichment culture ($N = 1038$)	Spa-type ($n = 746$)
Overall	0.07	0.02	< 0.001
Physical	0.06	0.04	< 0.001
School	0.02	0.01	< 0.001
Sports	0.12	0.29	< 0.001
Home	0.34	0.39	< 0.001
Other	0.08	0.06	< 0.001

Numbers represent P -values from t -tests. Statistically significant values highlighted in bold.

by both direct culture ($P = 0.002$) and enrichment culture ($P < 0.001$) (Figure 3). The probability of being a carrier increased by 3.7% (95% CI = 3.52–3.94; univariable logistic regression, result not presented) on increasing the friend circle by one *S. aureus* positive friend (defined by direct culture), as illustrated in Figure 4 and Supplementary Table 4. Similarly, the probability increased by 3.4% (95% CI = 3.33–3.45) for persistent carriage defined by enrichment culture (result not presented).

An adapted linear autocorrelation analysis gave results comparable to the logistic regression analysis (Table 5). The probabil-

ity of persistent carriage increased by 4.8% ($P < 0.001$) for each additional *S. aureus* positive friend defined by direct culture after adjusting for host risk factors. A similar increase of 6.0% ($P < 0.001$) was observed for the enrichment culture. The autocorrelation model also assessed the risk factors that made the participants friends significantly more contagious. For direct culture there was an association between sex, BMI and physical activity ($P = 0.001$ –0.008), and for enrichment culture there was an association between study program, BMI, and physical activity ($P < 0.001$ for all). Because of the assumptions of the autocorrelation model,

Table 4

Associations between host risk factors and transmission of *Staphylococcus aureus* persistent nasal carriage in the overall social network. Results from two different regression analyses producing "P-value" for the social effect of each characteristic and Relative risk for the comparison of risk of transmission between groups. Persistent nasal carriage determined by both direct culture and enrichment culture. The Fit Futures 1 study (N = 1038).

Risk factor (categories)	Direct culture			Enrichment culture		
	P-value	Relative risk	95% CI	P-value	Relative risk	95% CI
Sex						
Female	0.0002	1		0.027	1	
Male	0.999	0.845	0.805 - 0.884	0.843	0.937	0.900 - 0.974
Study program						
Vocational	0.548	1		0.353	1	
General	0.510	1.002	0.950 - 1.054	0.410	0.996	0.954 - 1.038
Sport	0.403	1.009	0.960 - 1.059	0.811	0.974	0.935 - 1.013
BMI ^a						
Underweight	0.793	0.953	0.905 - 1.001	0.841	0.968	0.928 - 1.008
Healthy	0.150	1		0.301	1	
Overweight	1	0.901	0.860 - 0.943	0.763	0.974	0.935 - 1.012
Obese	0.914	0.941	0.896 - 0.987	0.246	1.003	0.959 - 1.047
Smoke						
Daily	0.294	1		0.855	1	
Never	0.503	0.986	0.937 - 1.034	0.486	1.022	0.978 - 1.066
Sometimes	0.723	0.971	0.922 - 1.020	0.262	1.036	0.991 - 1.081
Snuff						
Daily	0.406	1		0.596	1	
Never	0.414	0.999	0.949 - 1.049	0.310	1.017	0.973 - 1.060
Sometimes	0.900	0.962	0.915 - 1.010	0.821	0.986	0.947 - 1.025
Alcohol						
≥ 2 per month	0.035	1		0.434	1	
≤ 1 month	0.806	0.933	0.885 - 0.980	0.602	0.991	0.948 - 1.034
Never	0.739	0.938	0.890 - 0.986	0.323	1.006	0.964 - 1.049
Physical activity ^b						
Light	0.301	1		0.089	1	
None	0.994	0.930	0.886 - 0.975	0.803	0.952	0.914 - 0.990
Medium	0.008	1.053	0.999 - 1.107	0.267	0.982	0.941 - 1.023
Hard	0.883	0.959	0.913 - 1.005	0.817	0.951	0.913 - 0.989
Hormonal contra-ceptives ^c						
Non-user	0.444	1		0.494	1	
Progestin	0.369	1.126	-0.230 - 2.482	0.392	1.239	-0.576 - 3.054
Low Estrogen	0.430	1.024	-0.414 - 2.264	0.475	1.046	-0.840 - 2.932
High Estrogen	0.476	0.940	-0.546 - 2.425	0.483	1.027	-0.862 - 2.916

P-values from comparison between random network against a random network with only that particular category. Participants with missing values are excluded from the analysis. Statistically significant values highlighted in bold.

Relative risk and 95% confidence interval (95% CI) from univariable logistic regression analysis.

^a BMI by kg/m². Underweight = <18.5; Healthy = 18.5-24.9; Overweight = 25.0-29.9; ≥ 30

^b Physical activity: None = reading, watching TV, or other sedentary activity; Low level = walking, cycling, or other forms of exercise at least 4 hours a week; Medium level = participation in recreational sports, heavy outdoor activities with minimum duration of 4 hours a week; High level = Participation in heavy training or sports competitions regularly several times a week.

^c Hormonal contraceptives: Non-user = No current use of hormonal contraceptives (women only); Progestin-only = Use of hormonal contraceptives with progestin (Cerazette, Nexplanon, Depo-provera, Implanon); Combination contraceptives low estradiol = Use of hormonal contraceptives with progestin and ethynodiol less than or equal to 20µg (Mercilon, Yasminelle, Loette 28, Nuvaring). Combination contraceptives high estradiol = Use of hormonal contraceptives with progestin and ethynodiol greater than or equal to 30µg (Marvelon, Yasmin, Microndynon, Oralcon, Diane, Synfase, Evra, Zyrona). Women taking contraceptives, but who were unable to recognize the brand were removed from the analysis

Table 5
Correlation between host risk factors and *Staphylococcus aureus* carrier status. Fit Futures 1 (N = 1038). Adapted multivariable linear autocorrelation model.

	Estimate ^a	SE	P-value
Direct culture			
ρ	0.048	0.011	<0.001
Sex	-0.048	0.028	0.0016
Study program	0.043	0.022	0.0542
BMI ^b	0.107	0.018	<0.001
Smoke	-0.012	0.027	0.650
Snuff	-0.001	0.020	0.968
Alcohol	0.038	0.021	0.066
Physical activity	0.033	0.012	0.008
Enrichment culture			
ρ	0.060	0.010	<0.001
Sex	-0.017	0.030	0.578
Study program	0.087	0.024	<0.001
Body mass index	0.085	0.019	<0.001
Smoke	-0.019	0.029	0.517
Snuff	0.001	0.022	0.950
Alcohol	0.070	0.022	0.002
Physical activity	0.046	0.014	<0.001

Significant values highlighted in bold.

^a Only estimates for the total model are valid. Beta estimates for individual host factors cannot be interpreted.

^b BMI = body mass index.

beta estimates for individual host factors could not be interpreted and sex-specific host factors (hormonal contraceptives) could not be included in the model. Females tended to have more relationships than males, which was also true for participants with normal BMI and participants with both medium and hard-level physical activity (Supplementary Table 3).

Discussion

In the present study, we demonstrated that social network is associated with *S. aureus* persistent-carrier status and spa type in a young population. This is, to our knowledge, the first study to analyze the transmission of *S. aureus* using social network analysis in a young population. We demonstrated that the probability of being a persistent carrier correlates with the number of close friends colonized with *S. aureus*. The autocorrelation analysis showed a 5-6% increased probability of *S. aureus* carriage with each additional *S. aureus* carrier friend. We also showed that friends tend to have the same spa types, indicating that the social network effect is partly driven by direct transmission of *S. aureus*. Our results coincide with former research that demonstrated comparable results in different cohorts (Gwizdala et al., 2011; Moldovan et al., 2019).

We analyzed different types of networks and found an association between transmission of *S. aureus* in the social network

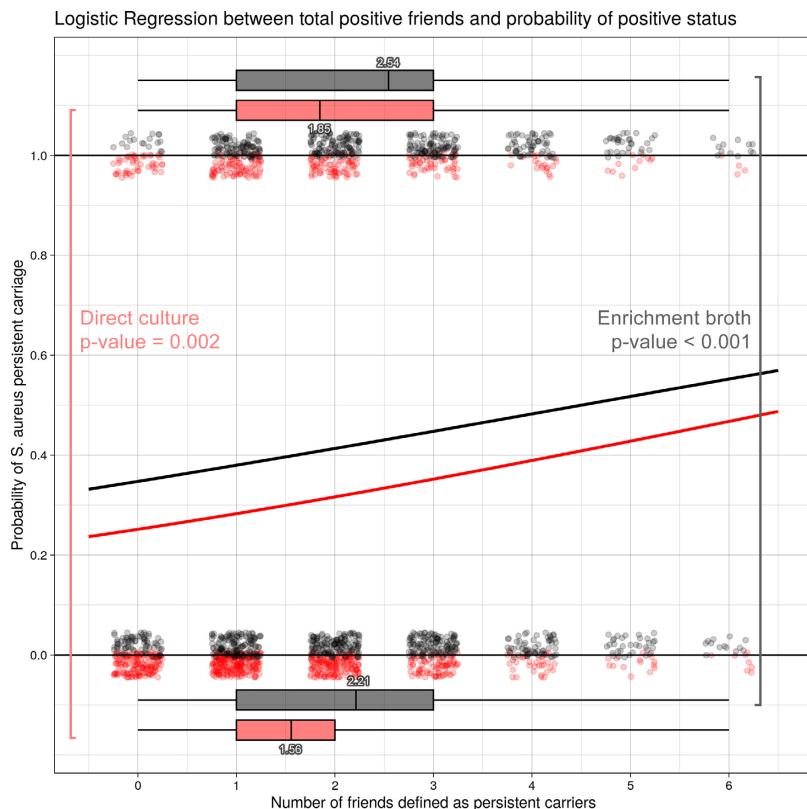


Figure 4. Probability of *Staphylococcus aureus* persistent nasal carriage with respect to friends' carrier status. Univariable logistic regression analysis. Fit Futures 1 ($n=1038$). Red color represents persistent nasal carriage defined by direct culture. Black color represents persistent nasal carriage defined by enrichment culture. The scatterplots show the distribution of persistent nasal carriers (along $Y=1$) and non-carriers (along $Y=0$) for sub-populations of students having from 0 to 6 *S. aureus* positive friends. Boxplots show the mean (middle line) and interquartile range (box limits) of *S. aureus* positive friends for persistent nasal carriers (at the top of the diagram) and non-carriers (at the bottom of the diagram). Outliers with more than 6 *S. aureus* positive friends are excluded from the figure, but did not affect the result ($N=3$). For more information see Supplementary Tables 6 and 7.

where participants confirmed they had physical contact (direct culture: $P = 0.07$; enrichment culture: $P = 0.04$). This might indicate that social contact is a key pathway for the spread of *S. aureus* in the community (Hogea et al., 2014), which is in line with former studies on transmission of *S. aureus* through a social network (Moldovan et al., 2019). Being together at school was also significantly associated with *S. aureus* transmission. We did not find any significant spread of *S. aureus* among students who were at home or participated in sports together.

There is also a substantial social dimension for several of the known host risk factors for *S. aureus* carriage, which suggests that social network effects may have contributed to associations observed in former studies. In a univariable logistic regression model, the risk of being a persistent carrier increased by 3.4–3.7% on increasing the friend circle by one *S. aureus* positive friend. A similar analysis (autocorrelation model) adjusted for host risk factors, showed an increase of 4.8–6.0%. The difference between the logistic

regression model and the autocorrelation model may partly represent the effect of the individual risk factors.

In our study, males had a higher prevalence of *S. aureus* persistent carriage compared to females which corresponds with previous studies (Knox et al., 2015; Mascaro et al., 2019). The social network analysis demonstrates that the female sex is the predominant social risk factor for carriage because of more relationships among females. This may substantiate the hypothesis of sex as a true biological risk factor for *S. aureus* carriage, as the male population has a higher prevalence of carriage while the relative risk of transmission is lower compared to the female population.

We also demonstrated increased transmission of *S. aureus* among students engaged in medium level physical activity in leisure time compared to those with sedentary leisure time. A former study showed an increased risk of *S. aureus* carriage in athletes doing contact sports (Mascaro et al., 2019). Many of the physical activities in youth are contact sports or close-counter train-

ing. In our population a higher percentage of women engaged in medium physical activity compared to men (women = 27% and men = 23%). The increased risk of transmission related to medium physical activity could therefore be partly attributed to the observed sex differences.

The use of alcohol more than twice a month was a social factor associated with the carriage of *S. aureus* by direct culture. This may reflect increased social contact with multiple friends at parties and social gatherings. Participants consuming alcohol more than twice a month had a higher number of friends than participants consuming less or no alcohol. We do not have information about the amount of alcohol consumed, and the alcohol variable is therefore lacking some precision. We also have some outliers that may have affected the results. We found no association between alcohol use and carriage defined by enrichment culture, this may be a result of a large number of statistical tests and the more homogenous variable with a high prevalence of *S. aureus* carriage for enrichment culture.

The autoregression model indicates an association between BMI and transmission of *S. aureus* in addition to sex, alcohol use, physical activity, and study program. The effect of friendship density might be partially related to body size, as students with normal BMI had more friends.

Excluding older outliers above 20 years ($n = 36$) from the network analysis did not affect the results, therefore all participants were included in the analysis. None of the interview questions on social networks provide information about the type or amount of physical contact. We also lack information on the total social network of the participants, including family and other social interactions outside school. Our model also lacks animal contacts and pets, that are known to influence transmission (Loeffler and Lloyd, 2010).

This will give a bias of unknown magnitude and direction. The social networks were constructed by self-reported information on social contacts one week before the study, and this could be misrepresenting of the participants' social contact over long periods of time. We therefore asked all participants to score the representativeness of the nominated friends, and 76 % of the participants claimed a score of five or above (on a scale from one to ten). We therefore believe the representativeness of the nominations to be high (Supplementary Figure 4).

We had complete spa-type data only from throat isolates, while nasal carriage is generally considered as the most clinically relevant phenotype. In a validation study of 100 participants with *S. aureus* isolated from cultures of two nasal and two throat swabs in FF1, 82 participants had the same spa type (data not shown). Therefore, we believe that our findings from social network analysis based on spa type of throat isolates also represent the transmission of nasal *S. aureus*. Another limitation is that we had 10 invalid nasal samples from the first swab and 51 invalid samples from the second swab. These were re-classified as negative for *S. aureus*. Because of the analysis of social networks, we believe that it would have introduced a larger bias in excluding parts of the social network compared with the bias of including potentially misclassified samples. The study was conducted between 2010–2011, and there may be some unknown bias in comparing results to present day. Although we believe that the prevalence of *S. aureus* is quite stable in the general population.

One limitation of defining the outcome of persistent nasal carriage is the number of swabs taken and use of Staphaurex plus agglutination test for *S. aureus* confirmation. Although the Staphaurex plus agglutination test could give false positive reactions for other staphylococci (van Griethuysen et al., 2001), we believe the combination of *S. aureus* selective CHROMagars and agglutination test increase sensitivity and specificity. Nouwen et al. proposed a "culture rule" that concludes that two nasal swabs taken at a week

interval can accurately classify *S. aureus* nasal carriage (Nouwen et al., 2004), but van Belkum et al. demonstrated a median survival of *S. aureus* of more than 154 days among persistent carriers, compared to 14 days among intermittent carriers and 4 days among non-carriers (van Belkum et al., 2009). Thus, it is likely that some participants were misclassified. Both limitations are classified as non-differential bias and therefore are more likely to give underestimations of results.

We reported results using both direct culture and enrichment. When enrichment broth is used, low bacterial loads are also detected, thereby giving an increased prevalence of *S. aureus* positive tests (Antri et al., 2018). In studies of decolonization, enrichment is recommended to prevent possible eradication failure (Diekema et al., 2011). The relevance of low bacterial load carriage in *S. aureus* epidemiology is not known, and most studies have used only direct culture. In this study, the results were similar for both definitions and might demonstrate the robustness of the findings.

Our analysis was modeled by using one time point, while interviews with the different participants were conducted at multiple time points. Most participants nominated friends who had the same attendance date as themselves, e.g., from their own school class (Supplementary Table 5). Furthermore, persistent nasal carriage is a relatively stable phenotype (van Belkum et al., 2009), and we therefore assume that time will not affect the present analysis.

In summary, our data from a general youth population supports social effects on *S. aureus* carriage and these result from both direct social transmission and shared lifestyle risk factors for carriage among friends. We demonstrated relationships between different social networks (i.e., overall, physical contact, school) and *S. aureus* persistent carriage and specific spa-types. We also showed that risk of transmission differs by host lifestyle factors. The male predominance in carriage is determined by sex-specific predisposing host characteristics, as social interactions among men are weak drivers of transmission compared with women. More studies are needed to further evaluate the interplay between the social environment and host risk factors in *S. aureus* carriage and should include household transmission and contact with animals.

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Ethical approval statement

Each participant signed a declaration of consent. Participants younger than 16 years had to bring written consent from a parent or guardian. FF1 was approved by The Regional Committee of Medical and Health Research Ethics North Norway (REK North, reference 2009/1282) and the Norwegian Data Protection Authority. The present study was approved by REK North (reference 2011/1710) and was conducted in accordance with the Declaration of Helsinki and national and institutional standards.

Author contributions

Anne-Sofie Furberg, Christopher Sievert Nielsen, Gunnar Skov Simonsen and Lars Ailo Bongo contributed with the conceptualization and design of the work. Anne-Sofie Furberg and Lars Ailo Bongo supervised the work. Johanna UE Sollid performed microbiological analysis of nasal and throat samples. Rafael A. Nozal Cañadas contributed with statistical analysis and statistical methods. Karina Olsen, Lars Småbrekke, Kristian Svendsen, Dina Stensen

and Anne Merethe Hanssen contributed in interpretation of data. Dina B. Stensen and Rafael A. Nozal Canadas wrote the original draft. All authors reviewed and approved the final manuscript. Rafael A. Nozal Canadas and Lars Ailo Bongo verify the underlying data.

Data availability

The data that support the findings of this study are available from The Fit Futures study but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon request and with permission of The Fit Futures study. Proposals for data should be directed to fitfutures@uit.no. Statistical analysis and consent form will be available on request. Proposals should be directed to dina.b.stensen@uit.no.

Declaration of Competing Interest

The authors have no competing interests to declare

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2022.08.018](https://doi.org/10.1016/j.ijid.2022.08.018).

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Social network analysis of *Staphylococcus aureus* carriage in a general youth population

Supplementary Material

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Statistical background

The use of Network analysis has increased exponentially over the last few years. In this brief introduction we include the statistical background on random graph analysis and autocorrelation networks models, and some included references to provide a deeper understanding of the topic.

In statistics, a general rule to solve problems is to find all possibilities and compare all the scenarios in which something happens against all scenarios in which something does not happen. Such a ratio will give you the probability of something occurring. In our case, it is impossible to compare random graphs with all possible random graphs to get the real probability. Such calculations are unattainable, and it is necessary to constrain the amount of possible random graphs based on some assumptions (1). The constraints added to the random graph will give a model which is similar enough to reality. In our case, we use the same frequency tables with a network with the same topology as constriction. We also assume that high contagiousness would cluster positives together with positives, and negatives together with negatives.

In this context, identical topology means having the same nodes (participants) and same edges (relationships) as the original network; but each node has randomly assigned attributes based on the probability distribution of each category (i.e., *S. aureus* persistent carrier status is assigned randomly to each node, following an arbitrary 30% prevalence probability, instead of using the original value).

Our bootstrapping (2) consists of counting how many relationships connect two nodes with the same attributes in our network (i.e., persistent carrier with persistent carrier or same *spa*-

types) in 1000 simulations. This gives us a distribution of 1000 values (with a mean and standard deviation) which we can compare to the real number of homophilic relationships in our network. We then perform simple hypothesis testing like t-test, where we consider a p-value of 0.05 or less to be statistically significant. As the numbers of these tests are low, there is no need for p-value correction for false positives.

Further, we can use the random network average number of relationships that we just created to compare with our network. We can create, again, a random network with the same topology, but using the conditional probability for each host factor independently. In this way we can check how much each of the categories deviates with respect to each other, and we can identify which category has higher or lower risk for the outcome variable.

Network autocorrelation models (3) are a special case of autoregression analysis in time series (4) where we want to find how much influence your neighbors (typically your social network of friends) have over you. We aim to find the ρ coefficient in the formula:

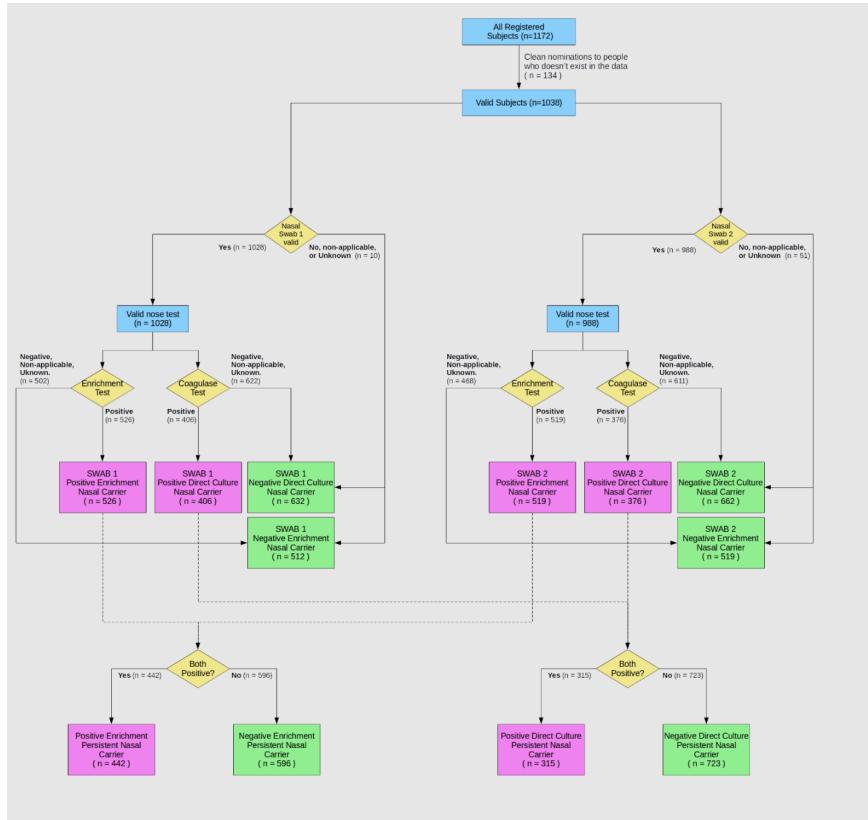
$$Y^{(t+1)} = \rho W_n Y^{(t)} + X\beta + \epsilon$$

W is a weighted matrix (typically normalized to 1) indicating which neighbors have influence over you, X is your explanatory variable (in our case, sex, BMI, smoke, and so on), β is a vector of coefficients (similar to linear regression) and ϵ is a random noise vector. Y is your dependent variable vector (in our case persistent carrier status), which over time (t), will converge to a common value. The ρ coefficient represents how much you are following the pressure of your neighbor influence and ranges typically from 0 to infinity, although negative values are also valid depending on your context. A value close to 0 would mean that you are completely ignoring your neighbors and the explanatory variables really do not have any influence on you. Positive values indicate that people can exert influence over you, and in our case, your friends will increase your risk of being a carrier.

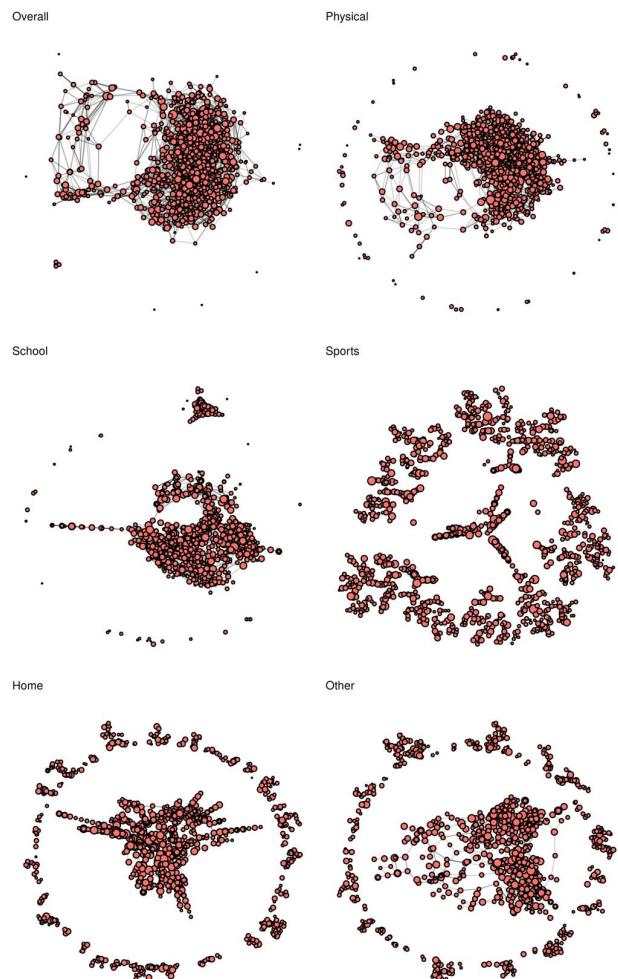
Significant negative values would indicate that you dislike your neighbors so much, that you will do the complete opposite of what he tells you to do. In our case, this is not a valid case for the ρ coefficient as you cannot protect someone from carriage, you simply will not transmit the bacteria. However, for the explanatory variables, negative values of ρ coefficient are valid in our case because we encode categorical variables with dummy variables.

References:

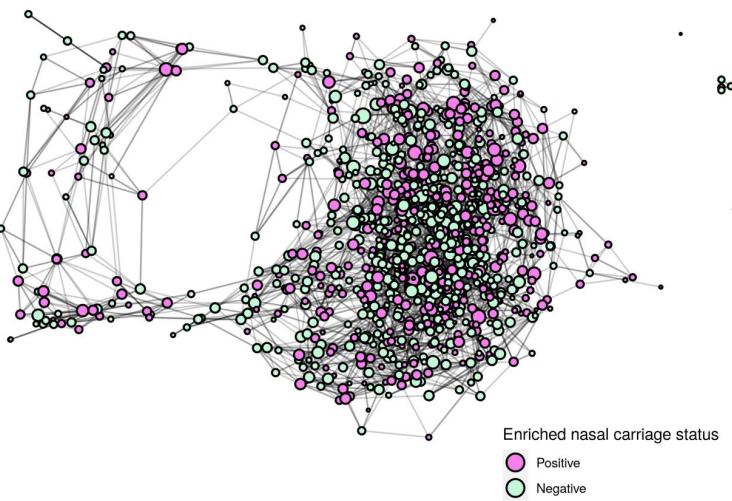
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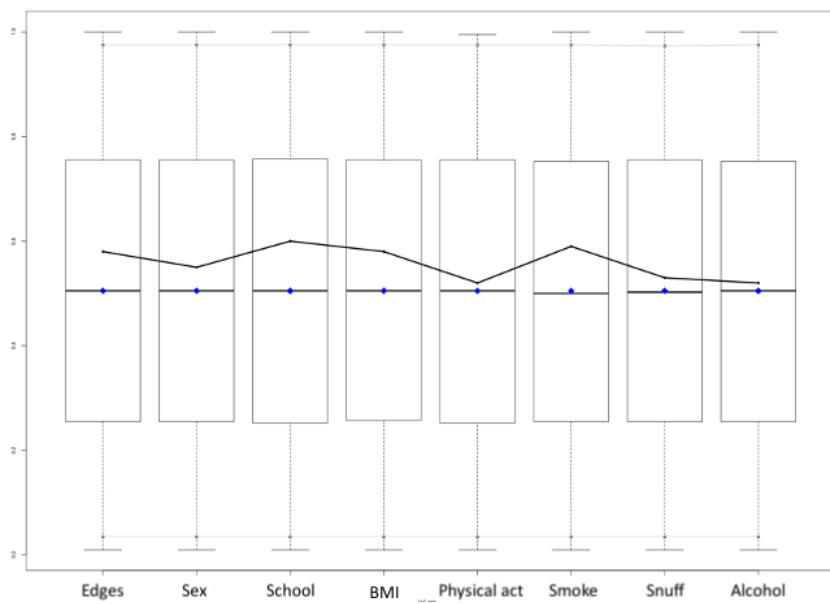
Supplementary Figure 1 Flowchart with inclusion criteria for definitions of *Staphylococcus aureus* persistent nasal carriage. The Fit Futures 1 study (N = 1038). Direct culture (bottom right) and enrichment culture (bottom left).



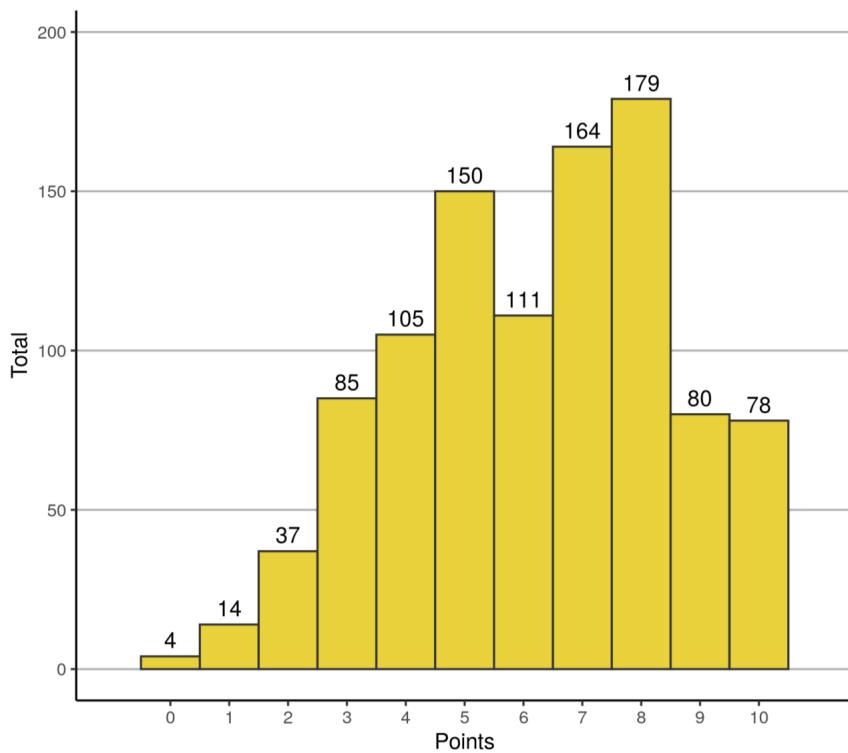
Supplementary Figure 2 Overview of the different social networks. The Fit Futures 1 study ($N = 1038$). From top to bottom and left to right: overall social network, physical contact, together at school, together in sports, together at home, and together in other settings. Each node represents a student. Each edge represents an undirected nomination (connection). The size of the node is proportional to the number of connections.



Supplementary Figure 3 Overall network. The Fit Futures 1 study ($N = 1038$). *Staphylococcus aureus* persistent nasal carriage status determined by enrichment culture is highlighted for each student (Positive = *S. aureus* detected in two nasal swab samples; Negative = *S. aureus* detected in one or none of two nasal swab samples). Node size is proportional to the number of connections (undirected friendship).



Supplementary Figure 4 Goodness of fit for the ERGM (Exponential Random Graph Model) analysis. The Fit Futures 1 study ($N = 1038$). Y-axis = proportion of statistics, X-axis = model statistics.



Supplementary Figure 5 Histogram of representativeness of the social network. The Fit Futures 1 study ($N = 1038$). 0 being not representative at all, and 10 being a perfect overview. For specific networks, having a mean score from top to bottom of school (6.61), other (6.52), physical (6.42) overall (6.29) sports (6.24) and home (6.13) (information not included in figure).

Supplementary Table 1 Characteristics of the study population by *Staphylococcus aureus* persistent nasal carriage determined by direct and enrichment culture. The Fit Futures 1 study (N = 1038).

	Direct culture			Enrichment culture		
	Positive ^d	Negative ^d	Prevalence	Positive ^d	Negative ^d	Prevalence
Sex	< 0.001			< 0.001		
Male	193	337	36.4 %	255	275	48.1 %
Female	122	386	24.0 %	187	321	36.8 %
Study program	0.99			0.08		
General	118	272	30.3 %	163	227	41.8 %
Sports	31	73	29.8 %	55	49	52.9 %
Vocational	166	378	30.5 %	224	320	41.2 %
Smoking	0.93			0.48		
Daily	14	34	29.2 %	24	24	50.0 %
Sometimes	59	129	31.4 %	76	112	40.4 %
Never	236	546	30.2 %	333	449	42.6 %
Snuff use	0.79			0.30		
Daily	73	172	29.8 %	107	138	43.7 %
Sometimes	43	88	32.8 %	63	68	48.1 %
Never	192	450	29.9 %	263	379	41.0 %
BMI category ^a	0.21			0.22		
< 18.5 kg/m ²	35	75	31.8 %	55	55	50.0 %
18.5-<25 kg/m ²	201	509	28.3 %	289	421	40.7 %
25-<30 kg/m ²	54	93	36.7 %	68	79	46.3 %
≥30 kg/m ²	22	45	32.8 %	27	40	40.3 %
Physical activity ^b	0.15			0.07		
None	80	149	34.9 %	107	122	46.7 %
Light	99	239	29.3 %	129	209	38.2 %

Medium	67	192	25.9 %	105	154	40.5 %
Hard	63	131	32.5 %	93	101	47.9 %
Alcohol intake			0.32			0.780
Never	88	192	31.4 %	115	165	41.1 %
<= 1 Month	134	286	31.9 %	183	237	43.6 %
≥2 Month	86	232	27.0 %	134	184	42.1 %
Hormonal contraceptives ^c			0.76			0.68
Non-user	78	249	23.9 %	121	206	37.2 %
Progestin only	3	17	15.0 %	5	15	25.0 %
Combination contraceptives, low estradiol	12	38	24.0%	19	31	38.0 %
Combination contraceptives, high estradiol	26	73	27.1 %	39	60	39.4 %

^a BMI = body mass index

^b Physical activity in leisure time: None = reading, watching TV, or other sedentary activity; Low level = walking, cycling, or other forms of exercise at least 4 hours a week; Medium level = participation in recreational sports, heavy outdoor activities with minimum duration of 4 hours a week; High level = Participation in heavy training or sports competitions regularly several times a week.

^c Hormonal contraceptives: Non-user = No current use of hormonal contraceptives (women only); Progestinonly = Use of hormonal contraceptives with progestin (Cerazette, Nexplanon, Depo-provera, Implanon); Combination contraceptives, low estradiol = Use of hormonal contraceptives with progestin and ethinyl estradiol less than or equal to 20µg (Mercilon, Yasminelle, Loette 28, Nuvaring). Combination contraceptives, high estradiol = Use of hormonal contraceptives with progestin and ethinyl estradiol greater than or equal to 30µg (Marvelon, Yasmin, Microgynon, Oralcon, Diane, Synfase, Evra, Zyrcona). Women taking contraceptives, but who were unable to recognize the brand were removed from the analysis.

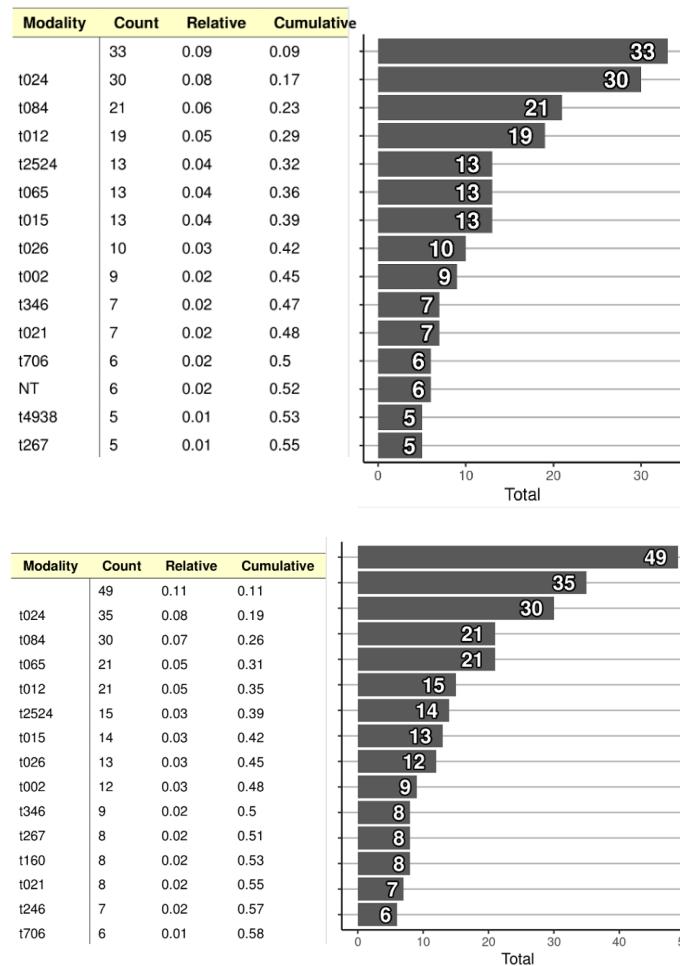
^d Positive = two consecutive nasal swab cultures positive for *Staphylococcus aureus* Negative = one or none of two consecutive nasal swab cultures positive for *Staphylococcus aureus*

Supplementary Table 2 ERGM (Exponential Random Graph Model) analysis of relationships within groups of participants with the same characteristics. The Fit Futures 1 study (N = 1038).

	Homophily (%)	Estimate (logit)	Std Error	P-value
Edges	--	-8.41	0.08	< 0.001
Sex	84.05	1.47	0.05	< 0.001
School	87.85	2.16	0.06	< 0.001
BMI ^a	54.23	0.18	0.04	< 0.001
Smoke	68.06	0.22	0.04	< 0.001
Snuff	57.71	0.31	0.04	< 0.001
Alcohol	45.26	0.42	0.04	< 0.001
Physical activity	40.22	0.43	0.04	< 0.001

^a BMI = body mass index

Supplementary Table 3 The most prevalent spa-types for *Staphylococcus aureus* throat carriage. The Fit Futures 1 study (N = 746). Only persistent carriers are shown. The plots are the results for the direct culture (above) and for enrichment culture (below).



Supplementary Table 2 Detailed summary of 1000 simulations for each social network. The Fit Futures 1 study (N = 1038).

Network	Total Relationships	Equal relationships	MIN	Q1	Median	Q3	MAX	SD	Direct culture P-value
Overall	3767	2260	2012	2136	2177	2214	2353	57	0.07
Physical	2823	1698	1492	1596	1628	1658	1756	45	0.06
School	2979	1814	1559	1687	1718	1747	1866	46	0.02
Sports	598	365	285	333	345	357	404	17	0.12
Home	1247	731	644	703	720	737	812	25	0.34
Others	1095	663	567	616	632	648	705	22	0.08
Network	Total relationships	Equal relationships	MIN	Q1	Median	Q3	MAX	SD	Enrichment culture P-value
Overall	3767	2013	1784	1899	1926	1953	2040	40	0.02
Physical	2823	1502	1339	1418	1442	1465	1576	34	0.04
School	2979	1610	1401	1499	1524	1548	1647	36	0.01
Sports	598	314	257	296	306	315	367	15	0.29
Home	1247	644	570	623	638	652	717	22	0.39
Others	1095	588	507	545	558	571	625	19	0.06
Network	Total relationships	Equal relationships	MIN	Q1	Median	Q3	MAX	SD	Spa-type P-value
Overall	1948	136	20	45	51	58	90	9.6	< 0.001
Physical	1459	111	16	33	38	44	84	8.0	< 0.001
School	1539	100	15	35	41	46	76	8.2	< 0.001
Sports	335	21	0	7	9	12	22	3.7	< 0.001
Home	664	63	4	14	17	21	38	5.1	< 0.001
Others	563	45	4	12	15	18	30	4.5	< 0.001

Columns 4-9^a contain the simulation summary statistics of the 1000 simulation result, in order, the minimum value of same-to-same relationships, first quartile, median rounded to the nearest integer, third quartile, maximum value, and standard deviation rounded to the nearest integer. The last column is the result of applying a t-test with the equal relationship against a distribution formed with the average of the 1000 simulations, and the standard deviation of the 1000 simulations. Significant p-values are highlighted in bold.

Supplementary Table 3 Average popularity in the overall network for each host risk factor.
The Fit Futures 1 study (N = 1038).

	Average Popularity ^a (3.62)	Relative physical isolation ^b (%)	Relative frequency all (%)
Sex	0.008		
Male	3.46	70	51.1
Female	3.81	30	48.9
BMI-category^c	0.001		
< 18.5 kg/m ²	3.61	9.23	10.60
18.5-<25 kg/m ²	3.72	62.31	68.40
25-<30 kg/m ²	3.63	14.62	14.16
> 30 kg/m ²	2.64	13.08	6.45
Smoking	0.003		
Daily	2.75	10	4.62
Sometimes	3.90	13.85	18.11
Never	3.60	72.31	75.34
Snuff use	0.003		
Daily	3.82	19.23	23.60
Sometimes	4.05	7.69	12.62
Never	3.45	69.23	61.85
Study program	0.004		
General	3.83	33.08	37.57
Sports	3.95	5.38	10.02
Vocational	3.43	62.31	52.41
Physical activity^d	0.254		
None	3.45	29.23	22.06
Light	3.56	30.77	32.56
Medium	3.73	21.54	24.95
Hard	3.80	14.62	18.69

Alcohol intake	< 0.001		
Never	3.05	41.54	26.97
<= 1 Month	3.76	30.77	40.46
> 2 Month	3.93	23.85	30.64
Direct culture persistent carriage	0.347		
Positive	3.72	30	30.35
Negative	3.59	70	69.65
Enrichment culture persistent carriage	0.007		
Positive	3.87	38.46	42.58
Negative	3.47	61.54	57.42
Hormonal Contraceptives (Women only, n = 505) ^e	Average Popularity (3.81)	Relative physical isolation (%)	Relative frequency all (%)
	0.006		
Non-user	4.00	58.97	64.88
Progestin only	2.65	13.16	3.97
Low Estrogen	3.44	13.16	9.92
High Estrogen	3.63	15.79	19.64
P-values are given next to variable names and represent a significant difference from the popularity average. P-values are calculated from t-test for two categories or ANOVA for more than two categories.			
^a Average popularity = Average number of friends nominating a participant as their friend			
^b Relative physical isolation = Number of participants not being nominated at all			
^c BMI = body mass index			
^d Physical activity: None = reading, watching TV, or other sedentary activity; Low level = walking, cycling, or other forms of exercise at least 4 hours a week; Medium level = participation in recreational sports, heavy outdoor activities with minimum duration of 4 hours a week; High level = Participation in heavy training or sports competitions regularly several times a week.			
^e Hormonal contraceptives: Non-user = No current use of hormonal contraceptives (women only); Progestin-only = Use of hormonal contraceptives with progestin (Cerazette, Nexplanon, Depo-provera, Implanon); Combination contraceptives low estradiol = Use of hormonal contraceptives with progestin and ethinyl estradiol less than or equal to 20µg (Mercilon, Yasminelle, Loette 28, Nuvaring). Combination contraceptives high estradiol = Use of hormonal contraceptives with progestin and ethinyl estradiol greater than or equal to 30µg (Marvelon, Yasmin, Microgynon, Oralcon, Diane, Synfase, Evra, Zyrcona). Women taking contraceptives, but who were unable to recognize the brand were removed from the analysis			

Supplementary Table 4 Average number of positive friends with respect to *Staphylococcus aureus* persistent nasal carrier status. The Fit Futures 1 study (N = 1038).

	Average number of friends	P-value ^a
Direct culture		0.002
Persistent carrier	1.85	
Non-carrier	1.56	
Enrichment culture		< 0.001
Persistent carrier	2.54	
Non-carrier	2.21	
^a Student's t-test		

Supplementary Table 5 Logistic regression model of *Staphylococcus aureus* persistent nasal carrier status with respect to positive friends. The Fit Futures 1 study (N = 1038).

	Estimate	Std Error	P-value
Direct culture			
Intercept	- 1.09	0.11	<0.001
Number of friends that are persistent carriers	0.16	0.05	0.0016
Enrichment culture			
Intercept	- 0.63	0.12	<0.001
Number of friends that are persistent carriers	0.14	0.04	<0.001

Supplementary Table 6 Attendance dates for each high school. The Fit Futures 1 study (N = 1038).

Week	Year	H1	H2	H3	H4	H5	H6	H7	H8	Friends
38	2010	32	0	0	0	0	0	0	0	64.79 %
39	2010	24	0	0	0	0	0	0	0	56.39 %
40	2010	36	0	0	0	0	0	0	0	47.82 %
41	2010	36	0	0	0	0	0	0	0	57.22 %
42	2010	35	0	0	0	0	0	0	0	49.29 %
43	2010	30	0	0	0	0	0	0	0	54.56 %
44	2010	6	16	0	0	0	0	0	0	42.80 %
45	2010	0	40	0	0	0	0	0	0	57.79 %
46	2010	0	42	0	0	0	0	0	0	62.78 %
47	2010	0	32	0	0	0	0	0	0	60.57 %
48	2010	0	6	0	0	0	0	0	28	60.69 %
49	2010	4	0	0	0	0	0	0	34	48.51 %
50	2010	4	4	0	0	0	0	0	31	39.06 %
51	2010	0	0	0	0	0	0	0	0	100.00 %
52	2010	0	0	0	0	0	0	0	0	100.00 %
1	2011	0	2	0	0	0	0	6	27	32.14 %
2	2011	0	0	0	0	0	0	43	0	61.51 %
3	2011	0	0	0	0	0	0	45	0	47.00 %
4	2011	0	0	0	0	0	0	40	0	47.87 %
5	2011	0	0	0	0	0	0	46	0	54.24 %
6	2011	0	0	30	0	0	0	10	0	45.17 %

7	2011	0	0	41	0	0	0	0	0	50.57 %
8	2011	0	0	44	0	0	0	2	0	56.52 %
9	2011	0	0	43	0	0	0	0	0	53.10 %
10	2011	0	0	0	0	0	0	0	0	100 %
11	2011	0	0	8	12	17	0	0	0	69.10 %
12	2011	0	0	0	4	18	19	0	0	54.51 %
13	2011	0	0	0	15	24	5	0	0	45.04 %
14	2011	0	0	0	22	26	0	0	0	43.44 %
15	2011	0	0	2	31	0	2	0	0	43.76 %
16	2011	0	0	0	0	0	0	0	0	100.00 %
17	2011	0	0	0	14	0	0	0	0	33.10 %
The first attendance date was 2010-September-20 th , which corresponds to Week 38 of 2010. The last attendance date was 2011-April-27 th , which corresponds to week 17 of 2011. Notice the public holidays in Norway, during weeks 51 and 52 of 2010 is Christmas holidays, and week 16 of 2011 is Easter holiday. H1 to H8 correspond to each of the high school identifiers. The "Friends" column shows the average proportion of friends nominated by each participant who attended the Fit Futures 1 study in the same week as the subject himself/ herself. The weighted average for all weeks is 52.07%.										

A.2 Paper B

The Social Sunshine of the Arctic Youth: Exploring friendship's influence on Vitamin D levels.

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ABSTRACT

Background: Vitamin D status correlates with 25OHD levels which depends on nutritional intake and UVB exposure. These two factors are influenced by friends, as people tend to participate in the same activities or eat a similar diet to their peers.

Objectives: Investigate how social interactions in a general high school population above the Arctic Circle influence 25OHD levels in the population.

Methods: The Fit Futures 1 study was performed over 8 months and interview data on social contact among 1038 first-level students in 8 high schools in Northern Norway were collected. Serum levels of 25OHD were measured ($n = 890$). The participants filled in a questionnaire about nutritional consumption, solarium habits, ethnicity, and chronic diseases. The participant's BMI was also measured.

Results: Once high schools' social biases were accounted for, only UVB radiation levels explained the differences in 25OHD levels. For non-solarium users, logistic regression analysis showed a positive correlation between a person's 25OHD levels and the 25OHD level of friends in the general population and within the same high school for most of the schools. We saw that women can influence other women into going to the solarium, while this influence was not present for men.

Conclusions: 25OHD levels can be influenced by social networks. This study can help to add weight to current public health recommendations due to the positive spillover effect in the network.

Keywords Network Analysis · Vitamin D · Social Influence

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1 Introduction

Humans tend to form friendship ties with individuals who are similar to them in certain aspects, referred to as homophily [1]. Although there is vast evidence that homophily shapes social networks, there is limited insight into how homophily functions in these networks. Most studies of homophily have been concerned with demographic variables such as age, sex, and social class. More recent evidence demonstrates deeper similarities among friends in behavior and personality [2]. Christakis and Fowler showed a spread of obesity through social ties [3]. If friends are more similar to one another in terms of healthy or unhealthy behavior, then social network proximity should be associated with similarity in biomarker profiles. Whether or not adolescents tend to associate with others who have similar lifestyles and experience similar lifestyle-related biomarker profiles has yet to be evaluated.

Vitamin D deficiency is emerging as a very common condition worldwide [4] and is associated with unfavorable skeletal outcomes, excess mortality, and a higher risk of infections. Serum 25-hydroxyvitamin D (25(OH)D) is considered to be the best biomarker of the body's vitamin D status and integrates Vitamin D derived from dietary intake and cutaneous synthesis after exposure to ultraviolet B (UVB) radiation of the solar electromagnetic spectrum. It has been estimated that the general European population gets 80-90% of its vitamin D from endogenous production in UVB-exposed skin. There is, however, considerable variation in this proportion across populations, population groups, and between individuals. Importantly, populations living at higher latitudes with periodic lack of photosynthesis may be at higher risk of vitamin D deficiency. Among a general youth population at 69°N participating in the Fit futures study, Tromsø Norway, 60% had vitamin D deficiency, defined by serum 25OHD below 50 nmol/l [5]. In the general adult population participating in the Tromsø Study, 19% had vitamin D deficiency, which is lower than the prevalence found in national data for Norway (28%) and in studies among adult populations further south [6–10].

Data from the Fit Futures and Tromsø study suggest that a sufficient level of serum 25(OH)D reflects several healthy lifestyle factors, such as outdoor activities, lower BMI, and fish-rich diet [5, 11], which may be defined by social interactions.

To our knowledge, no previous studies have been done on the effect of social networks in relation to vitamin D levels. Only one previous study has shown that poor economic factors influence health, because of the lack of vitamin D [12]. There has been a shift in social dynamics with indoor isolation during the COVID-19 pandemic, which showed how the severity of SARS-Covid-19 was linked to vitamin D deficiency [13]. Finally, ethnicity tends to be a strong social cohesion factor [14–26], and people of Middle Eastern, black, and South Asian descent require higher UVB levels and show higher deficiency prevalence than the white population [27–33]. Our objectives are to perform an explorative analysis in a general youth high school population to determine if social dynamics can affect 25OHD levels, and if so, to what extent environmental and lifestyle factors follow the same dynamics.

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2 Methods

2.1 Population and study design

The Fit Futures (FF) study [34] is a cohort with repeated health surveys among students from 8 high schools (H1-H8) in the Norwegian municipalities of Tromsø and Balsfjord (supplementary figure 4). FF1 was conducted from October 2010 to May 2011 (supplementary figure 5). All first-year students in the 8 high schools were invited (supplementary table 3), with consecutive inclusion of the eight schools. A total of 1117 youths were invited 93% attended, 508 girls (48.9%), and 530 boys. The age ranges from 15 to 28 years old, with 822 (79.2%) being 16 years or younger, and 52 (5%) older than 18 years. Students with special educational needs or mental disabilities are allowed to study for several years in high school in Norway.

The participants had a one-day visit to The Clinical Research Unit at the University Hospital of North Norway (UNN Tromsø), which included clinical examinations, microbiological samples, blood samples, an interview (self-reported social network, acute and chronic disease, medication, pregnancy), and a web-based general questionnaire. All procedures were performed by trained research nurses.

2.2 Social network assessment

The social network was constructed based on the following question: “*Which students have you had the most contact with the last week? Name up to 5 students at your own school or other schools in Tromsø and Balsfjord.*”. Reciprocity in the nomination was not mandatory. For each of the nominations, five “yes/no” questions assessed the type of contact they had with their nominations: “*Do you have physical contact?*”, “*Are you together at school?*”, “*Are you together at sports?*”, “*Are you together at home?*”, “*Are you together at other places?*”. This resulted in five social networks: Physical, School, Sport, Home, and Other. Adding all the relationships together formed the Overall Network. Illustrations for each network are presented in the supplementary materials (supplementary figure 6).

To evaluate if the friends mentioned were representative of the participant’s social network, the following question was asked: “*To what degree does this table of friends give an overview of your social network? Please indicate on a scale from 0 (small degree) to 10 (high degree).*” (supplementary figure 7).

2.3 Vitamin D assessment

Non-fasting blood samples were collected from an antecubital vein, and serum was separated and frozen at -70°C in the Fit Futures Biobank at the UiT The Arctic University of Norway. All serum samples (n = 890) were sent to the Hormone Laboratory, Haukeland University Hospital, Bergen, Norway; and 25OHD, 25OHD2, and 25OHD3 were analyzed by high-pressure liquid chromatography-mass spectroscopy (LC-MS/MS). A sample from all blood vials was reanalyzed at University College Cork, Cork, Ireland, by LC-MS/MS again as a part of the Vitamin D Standardization Project (VDSP) [35], and standardization was applied to the rest of the samples [36].

25OHD was used as a marker for vitamin D levels. This combines both sources of provitamin D + UVB, and D2+D3 from diet. It has a longer half-life span in blood than other available metabolites.

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In the analyses where categorical data is necessary, levels were defined as a binary variable dividing into vitamin D deficiency (< 50 nmol/L) or not vitamin D deficiency (≥ 50 nmol/L). In all cases, vitamin D toxicity is defined as greater than 150 nmol/L. [37–40]

25OHD levels are increased during pregnancy. All women who reported a possible pregnancy were given pregnancy tests, which all came back negative. The skin also loses the efficiency of synthesizing vitamin D with age [41], since the population is composed of young adults, no further analysis taking age into consideration was performed.

2.4 Diseases and medicine usage

There is a low prevalence of vitamin D absorption-impairing diseases, which are also heterogeneously distributed among the study population. Nobody in our population reported having bariatric surgery.

We have no significant number of students taking vitamin D-influencing medication such as anti-seizure drugs [42–44], steroid drugs [45–51], fat absorption reduction [45, 52–54], cholesterol metabolism modification [45, 55–57] or diuretics. The only anti-inflammatories drug [45–51], reported is “Ibuprofen 200mg” (n = 120), which does not affect the vitamin D level.

2.5 Melanin levels and ethnicity classification

The participants answered the question “*Do you consider yourself as...*”, with possible answers “Norwegian?”, “Sami”, “Kven / Finnish?” or “Other? (Please specify)”. Also, two questions regarding the country of birth of parents: “*Was your biological mother/father born in Norway? If not specify*”. These questions are summarized into a single variable with the ethnicity, or combinations of ethnicities, for each participant (supplementary table 6).

We combined all answers (n = 1018) into a single melanin quantity binary variable, dividing for assumed “Fair Skin” (996) for those of European, North American, or North Asia background, or mixing of any of these; and “Dark Skin” (22) for anyone with South American, African, South Asian, or any mixed background that included these. No conditions related to albinism or hyperpigmentation were self-reported in this population.

2.6 Solarium assessment

Visits to the solarium were recorded by the question “*Have you used a solarium during the last 4 weeks?*”. In Norway, access to solarium was restricted for teenagers from 2012, but not law-enforced until 2017 [58]. This data was gathered during 2010 and 2011 before any restrictions. Students were divided into solarium and non-solarium users according to their answers.

2.7 Nutritional information

There were 6 relevant questions regarding vitamin D intake. “*How often do you usually eat fat fish (e.g. salmon, trout, mackerel, herring)?*”, “*How often do you usually eat lean fish (e.g. cod, saithe, haddock)?*”, “*How much do you usually drink of whole milk, kefir and yoghurt?*”, “*How often do you usually eat cheese (all kinds)?*”, “*Do you take cod liver*

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oil, cod liver oil capsules or fish oil capsules?", "Do you use vitamin or mineral supplements?". All answers were classified as categorical variables, ranging from never to every day.

In Norway at the time of the study, fortification of food with vitamin D was only common in low-fat milk and flavored milk [59] (0.4 µg vitamin D per 100g) and for baby formula (0.48–0.72 µg/100 kJ) [60].

Cholesterol is an important precursor in the transformation of 7-dehydro cholesterol (pro-vitamin D3) into pre-vitamin D3 via UVB catalyzation. Our population shows overwhelmingly healthy levels of HLD, and LDL, and no significant number of diseases that might affect the liver cholesterol biosynthetic pathway.

2.8 Anthropometric assessment

Weight and height were measured using an automatic electronic scale (Jenix DS 102 stadiometer, Dong Sahn Jenix, Seoul, Korea) with participants wearing light clothing and no footwear. Body mass index (BMI) is calculated as weight (kg) divided by the squared height (m²) with no correction for sex or age.

2.9 Physical activity assessment

The participants stated their physical activity level according to four hierarchical levels using a slightly modified version of the Saltin-Grimby Physical Activity Level Scale [61].

"Exercise and physical exertion in leisure time. If your activity varies much, for example between summer and winter, then give an average" with possible answers *"Reading, watching TV, or other sedentary activity?"*, *"Walking, cycling, or other forms of exercise at least 4 hours a week? (including walking or cycling to place of school, shopping, Sunday-walking, etc.)"*, *"Participation in recreational sports, heavy outdoor activities, snow clearing etc? (note: duration of activity at least 4 hours a week)"* and *"Participation in hard training or sports competitions, regularly several times a week?"*. The answers are shortened into "None", "Light", "Medium" and "Hard" respectively for convenience.

A related question was *"How many hours per day do you spend by the PC, watch TV, DVD etc. outside school during weekends?"* with answers ranging from "None" to "10 hours or more".

2.10 Recreational drugs assessment

The use of recreational drugs was self-reported via the web-based questionnaire. For alcohol consumption, the question was *"How often do you drink alcohol?"*, with possible answers "Never", "Once per month or less", "2-4 times per month", "2-3 times per week", "4 or more times per week". Due to the low number of answers in some of the categories, "2-4 times per month", "2-3 times per week", "4 or more times per week" are all combined into "Twice per month or more". For smoking the question was *"Do you smoke?"* with possible answers "No, never", "Sometimes" and "Daily". For snuff use the question was *"Do you use snuff?"* with possible answers "No, never", "Sometimes" and "Daily".

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2.11 Natural UVB light, sun irradiance, and polar night

Tromsø and Balsfjord are located inside the Arctic Circle (60° N). The polar night started on the 23rd of November of 2010 and ended on the 19th of January 2011. During this time there is no sun irradiance. Solar irradiance above 60° N for 2011 is estimated to be about 8000 Wh/m^2 at its peak in July [62] (32.000 Wh/m^2 in the tropics at the same time [63]). After the polar night until the end of April, snow covers the ground; snow reflects UVB with about 86% efficiency. To determine which dates in our timeframe have relevant UVB, we estimated the duration of sun exposure to get 1000 IU of vitamin D synthesis. Assuming a clear day, snowy ground, type II skin, and 10% body exposure [64]: On March 1st it is not possible to acquire that amount. On March 15th it takes 5.22h. April 1st it takes 1.63h. On May 1st it takes 0.58h long. During autumn, assuming grass instead of snow, it is also not possible to acquire such an IU amount from October 1st.

Possible traveling was self-reported with the question: “*Have you been on a beach holiday during the last two months?*”, with only possible answers “Yes” and “No”. Traditionally, traveling might occur before high schools start near the end of August, in the nearly two weeks of winter break during Christmas, and a week during Easter break centered around the 24th of April in 2011. The data regarding traveling does not specify to which latitude, for how long, or estimate the grade of natural UVB irradiance.

2.12 Statistical Analysis

Statistical analyses were performed by using R version 4.1.2 and R Studio built 382.

Homophily, χ^2 tables, and bootstrapping with 1000 simulations were used to evaluate the similarities in solarium habits using a simple t-testing for theoretical same-to-same relationships against the simulated same-to-same relationships; as we have done in previous work [65]. Logistic regression was used to compare each person’s 25OHD levels (high/low) and the number of friends with high 25OHD levels. For both the general population, and for each high school individually.

χ^2 tables, two-sided Welch’s t-test when two categories are present, and a one-way ANOVA for the rest of the variables, were performed to determine statistically significant differences between groups. Bonferroni correction was applied for high numbers of multiple comparisons. Univariate regression models were used to compare relevant blood serum variables.

3 Results

3.1 Preliminary analysis of high school biases

There is a heterogeneous distribution of high or low melanin individuals across different high schools (supplementary table 6) with no significant bias ($p\text{-value} = 0.5$). The diet only has a bias in lean fish consumption ($p\text{-value} = 0.003$), with H1 and H8 consuming less than the expected frequency, and H3 and H4 consuming more than expected.

Blood extraction by date (supplementary figure 5) divides the school into Autumn 2010 (H1, H2), Winter 2010 (H3, H7, H8), and Spring 2011 (H4, H5, H6). Schools H2, H7, and H8 also have a significant number of students

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with blood samples taken during the polar night. H1 and H6 show a bias towards sunbathing traveling (supplementary table 14). H1 was the first school to be tested so it is expected that students had recent travels due to the summer holiday. H6 students are expected to travel more related to training or competitions. The differences in 25OHD levels between solarium and non-solarium users are described further down.

3.2 Population levels of vitamin D

Previous studies done within the same population have shown an increase of 25OHD levels associated with vitamin and mineral supplements, physical activity, sunbathing holidays, and use of solariums for both sexes, while only men showed increased levels for the use of snuff, consumption of fortified milk, and fish liver oil [5]. Other studies in the general Tromsø population have shown that vitamin D has been positively associated with older age, blood sample time collection, sunbathing holiday, higher alcohol intake, use of fish oil and vitamin supplements, and negatively associated with smoking and obesity [66]. Adolescents in Tromsø have a higher prevalence of vitamin D deficiency compared with a similar-aged population in Spain [67]. We show 25OHD levels for comparison across categories of all variables of interest (table 1), however, the relevant variables in the general population do not seem to be relevant once we analyze high schools one by one.

“Solarium visit in the last 4 weeks” shows a dramatic difference in vitamin D deficiency between people who visit solariums (27.1%) and people who do not (70.7%). As such, all further analysis regarding high school bias is performed using only people who do not go to the solarium (supplementary tables 8, 9, 10, 11, 12 and 13).

“BMI” is known to be a risk factor for vitamin D levels. Fat cells can sequester vitamin D due to being a fat-soluble vitamin, and it is not surprising to find lower levels for higher %fat individuals. This population has a similar BMI for both men (22.51 ± 4.22) and women (22.62 ± 4.24) in the total population and for men (22.61 ± 4.38) and women (22.89 ± 4.48) in the non-solarium population. However, BMI is not evenly distributed across high schools for non-solarium users (p-value < 0.0001). There is a higher prevalence of obesity in H2 and H5, overweight in H8, and underweight in H4. H7 has a lower prevalence of overweight and obese individuals. All H6 students fall into the “Healthy” BMI category. H6 total number of students is low, and the p-value to ascertain a non-random habit is not significant. However, H6 is exclusively a sports high-school so it is likely that they are biased towards a healthier lifestyle even though the binomial test for this variable cannot suggest so.

“Sex” differences are partially explained because women visit the solarium more often than men and this influence will be discussed later. High schools are biased with respect to the sex distribution (p-value < 0.0001), with H1 and H8 leaning toward men, and H2 and H3 leaning toward women.

Recreational drug consumption also shows a strong bias towards high school for alcohol, smoking, and snuff habits (p-value < 0.0001 for all cases). Schools that show a pro-smoking bias are H1, H2, H5, and H8. Schools that show a pro-snuff bias are in H1 and have very strong usage in H8. Schools that show a pro-alcohol bias are H5 and very strong in H8. Anti-alcohol bias is shown in H6. Anti-snuff bias is shown in H7, and very slightly in H3 and H6. There seems to be no “no smoking” bias, but smoke frequency is lower in H3, H4, and H7. In H6 nobody smokes, but once again the p-value is not low enough to suggest a non-random habit, although H6 is a sport school so it is likely that they avoid smoking.

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Physical activity also shows a bias with respect to high schools ($p\text{-value} < 0.0001$). With H2 and H8 leaning toward none, H1, H3, and H5 toward light to medium, and H6 and H7 toward hard.

Finally, we stratify all non-solarium users by high schools and run a two-sided Welch's t-test when two categories are present, and a one-way ANOVA for the rest of the variables. After correcting all results for multiple testing with Bonferroni, "Sex" was relevant for H8 ($p\text{-value} = 0.0059$, {men $n = 59$, $x = 28.45 \text{ nmol/l}$; women $n = 19$, $x = 46.34 \text{ nmol/l}$ }), "Physical Activity" for H3 ($p\text{-value} = 0.03$, {none $= 24$, $x = 30.89 \text{ nmol/l}$; light $n = 44$, $x = 40.14 \text{ nmol/l}$; medium $n = 42$, $x = 49.47 \text{ nmol/l}$; hard $n = 19$, $x = 51.2 \text{ nmol/l}$ }). "*Holiday / Sunbathing in the last 2 months*" was only significant in H1, first school to be tested after summer, and H3, first school to be completely tested after Christmas.

3.3 Similarities in solarium habits among friends

Women in the general population have higher vitamin D levels across the year (table 1 and figure 1), this also happens with people going to the solarium (table 1 and figure 2). We checked χ^2 tables for diet and solarium habits to test differences between men and women. The diet table showed no significant differences in diet, but significant differences in solarium habits were found ($p\text{-value} < 0.0001$) (table 2). Men tend to not go to the solarium (33.64% of the solarium population) while women tend to go to the solarium (66.46%). This might indicate that social relationships between men and women groups affect solarium habits.

Sex is a strong homophily variable defining friendship (84.05%), and men are friends with mostly men (72.06%) and women are friends with mostly women (72.89%). Our previous studies [65] on the data also show that men have fewer friends (3.37) on average than women (3.85) ($p\text{-value} = 0.02$). The homophily for solarium visitors is 68.36%, with "yes" having a homophily of 22% but not significant, and "no" having a 66% (8% lower than it should) with $p\text{-value} < 0.0001$. This means that people who do not go to the solarium are less likely to form friendships with each other. Moreover, it correlates with the sex dynamics of men having fewer friends, and men not going into the solarium as often.

We compared the social network against simulated networks to check if people going to the solarium influence other people into going to the solarium. For this analysis, we filtered out people who did not answer the question about the solarium ($n = 33$). Instead of the original 3767 relationships, we were left with 3575 relationships in total. Doing 1000 simulations we got an average of 2365 same-to-same relationships with a significance of $p\text{-value} = 0.008$ for the overall network. This indicates that people are biased and relationships with respect to solarium habits are non-random. We tried the same analysis again using only same-sex friends. Sex has very high homophily, as such we believe that barely any influence from men to women and vice-versa is lost in this analysis. For women, the total same-to-same relationships are 1049 with a $p\text{-value}$ of 0.0002 which seems to indicate that women tend to form groups of friends with the same solarium habits. For men, however, we have 1122 same-to-same relationships, resulting in a $p\text{-value}$ of 0.23, showing no bias in this case.

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Table 1: Descriptive statistics with respect to all variables of interest. In the column "Variable" we show the population composition, the column "All" is the analysis of the whole population without missing values, and the column "Non-solarium only" represents the population that did not go to the solarium in the last 4 weeks. In "Variable", we show the categories of each variable (i.e.: Man, Woman in Sex), the absolute frequency of each category (n), and the relative frequency of each category (f). In both "All" and "Non-solarium only", we show the absolute frequency of people with valid 25OHD values (N), the average for each category (Average), how many values are below 50 nmol/l (N<50), and the relative frequency in each category of people with low vitamin D (F). To calculate the p-values we run a two-sided Welch's t-test when two categories are present, and a one-way ANOVA for the rest of the variables. Relevant variables and p-values are highlighted in bold. The Fit Futures 1 study.

Variable	All			No solarium only		
	n	f	N	Average	N <50	F
Solarium visit in the last 4 weeks						
Yes	217	0.209	199	66.62	54	0.271
No	78	0.759	711	40.79	503	0.707
<Missing values>	33	0.002				
Holidays / Sunbathing last 2 months						
Yes	77	0.074	73	62.05	22	0.286
No	928	0.894	836	45.12	533	0.638
<Missing values>	33	0.002				
P-value = <0.0001						
BMI						
Underweight	110	0.106	102	44.02	67	0.657
Healthy	710	0.684	647	49.09	368	0.569
Overweight	147	0.142	129	42.59	85	0.659
Obese	67	0.065	59	33.81	49	0.831
<Missing values>	4	0.004				
P-value = 0.0005						
General Health						
Very bad	7	0.007	7	57.87	3	0.429
Bad	53	0.051	49	48.10	26	0.531
Neither good nor bad	218	0.21	195	48.35	117	0.600
Good	497	0.479	458	45.60	286	0.624
Excellent	241	0.232	210	47.49	124	0.590
<Missing values>	22	0.021				
P-value = 0.4						
Smoke						
Never	782	0.753	716	46.80	430	0.601
Sometimes	188	0.181	165	47.45	99	0.600
Daily	48	0.046	42	42.58	31	0.738
<Missing values>	20	0.019				
P-value = 0.469						
Snuff						
Never	642	0.618	590	46.79	356	0.603
Sometimes	131	0.126	116	51.87	61	0.526
Daily	245	0.236	217	43.81	143	0.659
<Missing values>	20	0.019				
P-value = 0.009						
Alcohol						
Never	280	0.27	260	45.10	166	0.638
Once per month or less	420	0.405	374	47.16	226	0.604
Twice or more per moth	318	0.306	289	47.62	168	0.581
<Missing values>	20	0.019				
P-value = 0.397						
Physical Activity						
None	229	0.221	202	35.30	106	0.822
Light	381	0.372	301	45.23	195	0.646
Moderate	259	0.25	238	50.88	124	0.521
Hard	194	0.187	184	56.08	77	0.418
<Missing values>	18	0.017				
P-value = <0.0001						
Screen Time						
			N	P-value = 0.801		
About half an hour or less	43	0.041	40	56.05	21	0.522
About 1 to 1.5 hours	174	0.168	156	45.77	94	0.603
About 2 to 3 hours	38	0.372	351	47.03	213	0.607
About 4 to 6 hours	324	0.312	280	47.36	174	0.602
About 7 to 9 hours	68	0.066	63	43.83	41	0.651
10 hours or more	22	0.021	20	46.65	12	0.600
<Missing values>	21	0.020				
P-value = <0.0001						
High School						
			N	P-value = <0.0001		
H1	207	0.199	180	42.59	122	0.678
H2	142	0.137	121	42.39	84	0.694
H3	168	0.162	159	47.3	95	0.597
H4	98	0.094	92	47.27	50	0.543
H5	85	0.082	71	46.54	46	0.648
H6	26	0.025	24	63.68	7	0.292
H7	192	0.185	181	53.51	91	0.503
H8	120	0.116	111	41.64	76	0.683
P-value = <0.0001						
Skin type						
			N	P-value = 0.0114		
Fair	996	0.960	904	47.06	543	0.545
Dark	22	0.022	20	30.41	18	0.900
<Missing values>	20	0.019				
P-value = 0.0181						
Variable						
			N	All		
					No solarium only	

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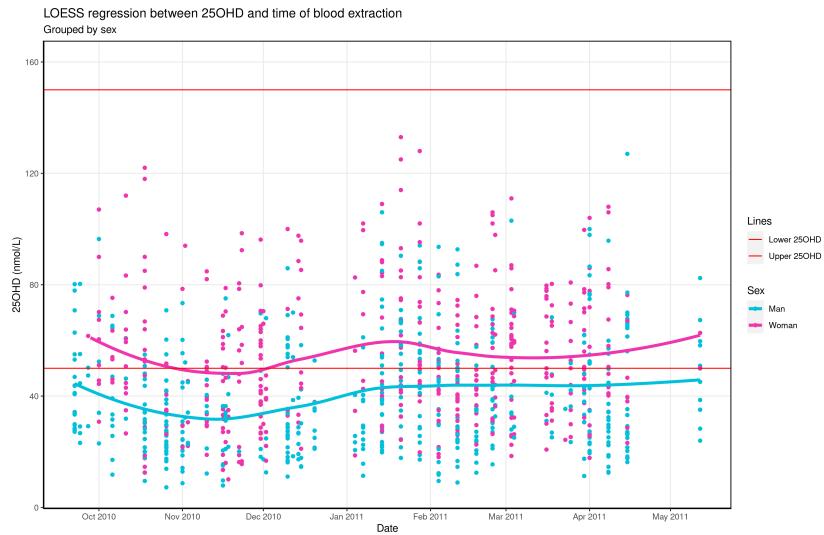


Figure 1: 25OHD levels from October 2010 to May 2011 divided by sex. Horizontal red lines mark the boundaries of healthy 25OHD levels. Women display higher levels than men across the whole year. The Fit Futures I study, N = 890.

Table 2: χ^2 table for “Did you go to the solarium in the last 4 weeks?” (yes/no), and sex. The header numbers indicate the total population absolute and relative frequency for men and women. The lower marginals are how many of these have available data with respect to the solarium question. Each inner cell is divided into 3 parts; the left-most is the total number of relationships in this combination, the center one is the expected number of relationships, and the right part contains an arrow indicating over (up) or underrepresented (down) using a two-sided binomial test with at least p-value < 0.1. Women are biased toward the yes answer, while men are biased towards the no answer. The Fit Futures I study.

$\chi^2 < 0.0001$	Man		Woman		Total	Freq
	n = 530 , f = .51	n = 508 , f = .49				
Yes	73 (106)	↓	144 (103)	↑	217	21%
No	436 (386)	↑	352 (376)	↓	788	76%
Total	509		496		1005	
Frequency	49%		48%			97%

3.4 Social influence in 25OHD

We want to check if non-solarium students with high 25OHD levels influence other non-solarium students to have high 25OHD levels as well by using logistic regression. The result shows that the chances of having high vitamin D increase by 7.25% [5.65%, 8.85%] for each additional friend who also has high vitamin D (figure 3). This result however can be biased. For example, different high schools had different blood extraction dates around the year, and friendship has very high homophily for high school (87.5%), so it is possible that we are just measuring high schools with higher density connections, while those schools coincidentally extracted blood at peak or bottom sun irradiance.

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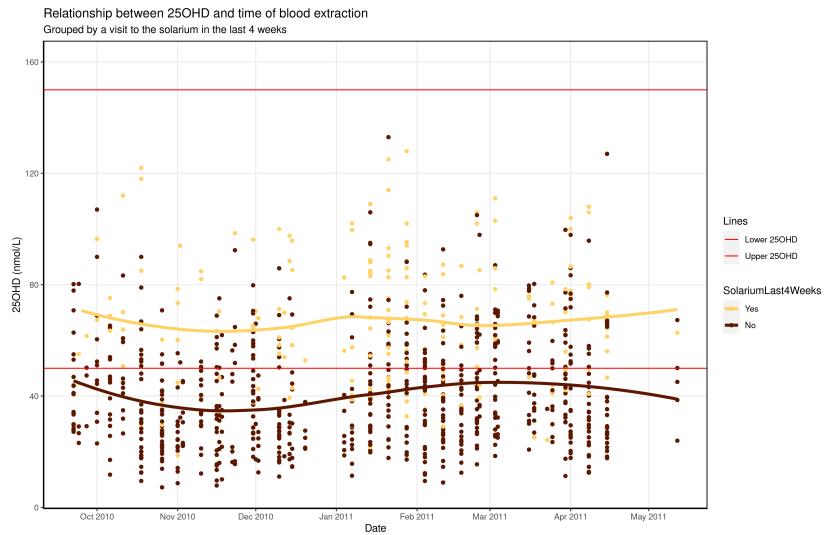


Figure 2: 25OHD levels from October 2010 to May 2011 divided by solarium habit. Horizontal red lines mark the boundaries of healthy 25OHD levels. People going to the solarium display higher levels than people who don't go to the solarium across the whole year. People who don't go to the solarium display a dip in levels in December while a peak of levels in near April. There was a second dip in the middle of May due to a small sample size and low vitamin D levels of students who were tested at that time. The Fit Futures I study. N = 890

We repeated the logistic regression analysis for each high school independently. Five of the eight also showed statistically significant 25OHD differences (figure 3) (H3, H5, H6, H7, and H8), with two having blood extraction during the polar night (H7 and H8). This suggests that friends influence each other into sharing certain lifestyles which makes 25OHD levels similar.

Furthermore, we plotted each student's 25OHD level against his or her friends' average of 25OHD. We see a weak correlation ($R^2= 0.1$, p-value < 0.0001) among the whole population (supplementary figure 17). The same analysis of each individual high school shows more relevant results for H2, H5, and H8 (supplementary figure 17). We also performed another 1000 simulations for each high school individually, for non-solarium users only, and found non-random friendship based on vitamin D status for H1, H2, H3, H4, H5, and H8 (supplementary table 5).

3.5 Levels by nutritional data

Finally, we wanted to check if the diet was influenced by friends. Performing ANOVA in all our nutritional variables showed no 25OHD significance difference between consumption groups for fat fish, cheese, dairy, vitamin pills, or even fish oil complements. Analyzing each high school independently, we found no correlation at all in any of the 48 possible combinations without even applying any post-hoc correction. The only difference present was in the consumption of lean fish in the general population, however, the difference was only between lower-frequency consumption groups and

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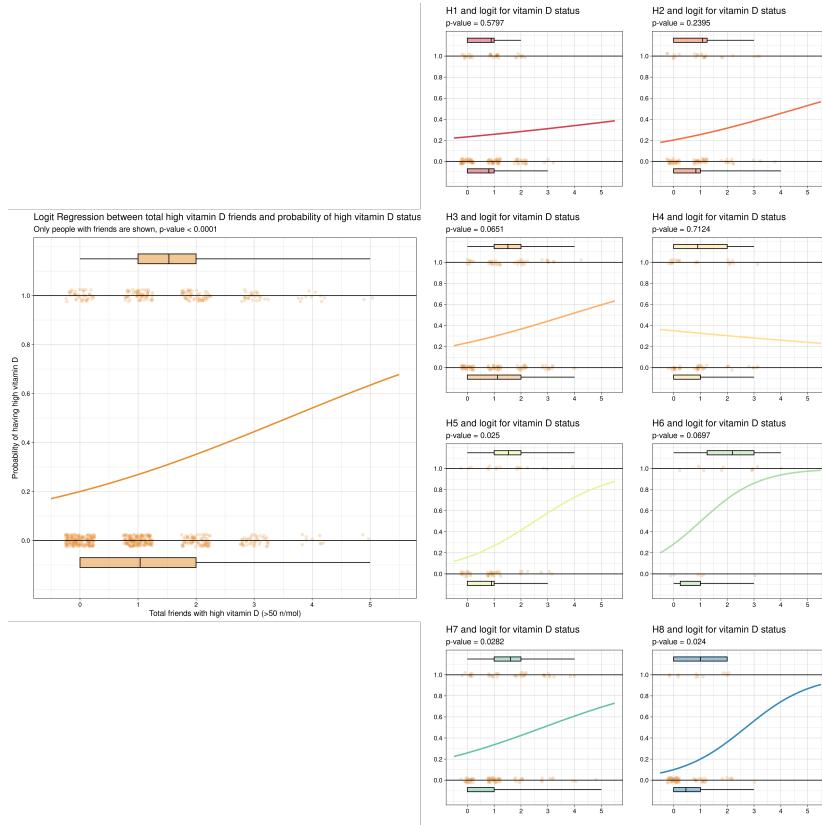


Figure 3: (Left) Logistic regression with respect to 25OHD levels between each person and high 25OHD friends. Each dot represents a person who does not go to the solarium, and who has at least one friend. The dots are laid out on the Y-axis in 1 if the subject has high vitamin D (25OHD $> 50 \text{ nmol/l}$), or 0 if low vitamin D (25OHD $< 50 \text{ nmol/l}$). In the X-axis we count how many high vitamin D friends this person has. The boxplots represent the difference in the number of high vitamin D friends between people who have low vitamin D (0) or high vitamin D (1). People with low vitamin D have an average of 1.04 friends with high vitamin D, while people with high vitamin D have an average of 1.53 friends with high vitamin D (p-value < 0.0001). (Right) The logistic regression analysis was performed for each high school independently. Each plot has a p-value displayed under the title. Relevant levels are for H3, H5, H6, H7 and H8.

the middle-frequency consumption groups, while the high-frequency groups show approximately the same levels of 25OHD as people not eating any lean fish. We believe that this is the effect of confounding variables between lean fish frequency and 25OHD. We also tried to perform the same 1000 simulations for each of the 6 food groups in the overall network and we found no evidence that friends influence dietary habits among each other.

4 Discussion

4.1 Social influence of high school in vitamin D levels

Among the variables of sex, BMI, recreational drugs, health, solarium, and sports habits, high school has the stronger homophily when it comes to friendship (min 70% per school). We see that women tend to form friendships with other women if they share the same solarium habits. In previous works [58] the main motivation of Norwegian teenagers for going to the solarium was “*To get a tan*” with nearly 80% for girls and 60% for boys in both 2016 and 2017, followed by “*To prepare for holidays*” 32% in girls and 16.3% in boys in 2016, and near 23% for both in 2017. “*To make vitamin D*” appears as the third motivation with 20% for both in 2016 and 17.5% for both in 2017. It should be noticed that previous work showed that none of these reasons are justified due to solariums being too powerful, having the wrong UVA/UVB ratio, not increasing protection, and increasing hypervitaminosis D [55, 58, 68–70].

For non-solarium users, it appears that there is a general tendency in the population in which students who have a higher number of friends with high vitamin D levels tend to have higher vitamin D levels themselves. This tendency is also present in 5 of the 8 high schools. The simulations and the regression models also show a tendency to have similar vitamin D levels compared to friends. This accounts for possible bias towards total UVB. Furthermore, skin tone seems to be homogenously distributed across high schools, and the total number of dark-skin individuals is low (2% population) so this effect is not due to having an unbalanced skin type distribution. In our data, there seems to be no bias towards diet in any school other than lean fish consumption. Lean fish does not contain significant levels of vitamin D, and higher 25OHD levels in this consumption group appear to be due to confounding factors.

This seems to indicate that people follow the same healthy or unhealthy habits related to vitamin D absorption as their friends. This might include socio-economic factors such as being able to afford more traveling to more sunny areas, being more physically active and spending more time outdoors, having better diets that are rich in fatty fish, or better education related to vitamin D deficiency and supplementation.

4.2 Confounding of high school in vitamin D levels with other factors

H8 is the school with the lowest average 25OHD levels and is biased towards all the variables with lower-than-average 25OHD levels (males with -9.44 nmol/l 25OHD lower than women, not eating lean fish -5.71, alcohol consumption -3.49, smoking -6.7, snuff -6.91, and no physical activity -10.93). H1 is a similar school with no bias towards alcohol, and bias towards light physical activity; that despite having more traveling than any other school, is tied at second place with lower 25OHD levels. These two schools have 31% of the student population. In contrast, H6 and H7 are the complete opposite, with the highest vitamin D levels of any school, and bias towards no alcohol, no smoke, no snuff, and hard physical activity. Both H6 and H7 alone represent 21% of the population. Studying these variable levels for each high school independently, among students that do not go to the solarium, shows only 4 significant values after Bonferroni correction. H8 for sex, H3 for physical activity, and H1 and H3 for traveling.

Non-solarium women in H8 have +13.77 nmol/l average vitamin D levels than their male counterparts. These women do not show different habits than men in diet, BMI, physical activity, or recent sunbathing. This school has a bias towards the male student population, but neither sex displays different social dynamics that differ significantly from any other school. A network plot from the non-solarium population in H8 (supplementary figure 16), confirms the

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logistic regression analysis and shows a pattern in which women with high vitamin D are friends with other women with high vitamin D, low vitamin D men are friends with low vitamin D friends, and high vitamin D men are friends with high vitamin D friends. Therefore, a proper follow-up of the students in this school can help to understand what helped these women to gain much better levels than their male counterparts, which is of particular interest given that H8 blood samples were taken in the middle of the polar night. A possible explanation is the use of oral contraceptives with estrogen [71], which are common in this school. However, in this school, we found no 25OHD significant difference between women not going to the solarium using Microgynon ($n = 8$) and those not using oral contraceptives ($n = 9$). The rest of the network plots, for all other high schools, also show clusters of non-solarium men or women with similar 25OHD levels in accordance to the simulation results (supplementary figures 9, 10, 11, 12, 13, 14, 15)

Physical activity (PA) in H3 is the only place where this variable is significant. PA is linked to outdoor sports and activities. However, Tromsø is cold and has a daily average temperature ranging from an average of 7.8°C in September to -3.3°C in February. Due to both clothing and lack of UVB, it is very unlikely that people in this school are exposed to enough skin to get enough UVB on a daily basis. However, it is likely that people doing physical activity have a healthier diet. Evidence suggests that obese people require higher vitamin D [72, 73], so physical activity PA is recommended to lower the vitamin D requirements regardless of whether it helps absorption or not.

Traveling to southern latitudes also helps with the UVB levels in H1 and H3. However, we do not have refined data regarding the amount of time of sun exposure, latitude, or possible skin lesions during that time to make a proper assessment. Further data is needed to evaluate the risk-benefit relationship of sun exposure with respect to gains of vitamin D in this particular population. Food fortification seems to have helped with lowering cancer mortality rates in Europe [59], and will be a safer public health approach than recommending increasing UVA+UVB exposure.

Altogether the results from the present analysis indicate that the only good predictor of vitamin D levels in this population is UVB radiation absorption due to associations with the date of the year, traveling, or solarium usage, and the significance of vitamin D with respect to these variables stems from the biases present in high school social dynamics.

4.3 Contradictory results and studies

We showed that getting closer to people with high vitamin D levels tends to increase vitamin D levels in the individual. This is of course due to similar interests to those lifestyles of peers, and we have shown extensively the effects it has in different high schools. However, due to the limited nutritional data and PA estimates, we cannot ascertain the effects that each possible healthier lifestyle may have on the network.

Vitamin D research presents contradictory evidence in many studies. This might be due to 25OHD tests not being properly standardized and poor experiment design [7, 74, 75] or not accounting for other supplements [76, 77]. Our study also adds to the confusion regarding the effective sources of vitamin D. For dietary habits in each school independently, or in the total population, there are no significant differences in vitamin D levels with neither fat fish consumption, and for daily intake of fish oil pills that typically contain 500-1.000 UI of D₃ per pill. It is very unlikely that people reporting taking these pills do not display higher levels. For example, an interventional study in Northern Ireland with university students showed that daily supplements of 600 IU increased by almost +40nmol/l with respect to

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the control group [78]. Our dataset uses memory-based dietary assessment methods (M-BMs), described as "*uncritical faith in the validity and value of M-BMs has wasted substantial resources and constitutes the greatest impediment to scientific progress in obesity and nutrition research*" [79]. Similar conclusions can be found in self-reported data in the geriatric residential population [80]. Other studies suggest that the validity of Automated Self-Administered 24-hour recalls (ASA24s) is good enough [81] and multiple ASA24s and 4-d food records (4DFRs) provided the best estimates [82]. Our students report on food-frequency questionnaires (FFQs), which vary from the last 24 hours of food consumption prior to blood extraction, which was not even taken after 8 hours of fasting. It is important to enhance the scrutiny of dietary intake in future epidemiological studies. As such, we believe using FFQ is not a good option, and at the very least, having a nutritional professional oversee the ASA24s. Ideally, 4DFRs should be inputted into a food database (such as <https://www.matportalen.no/>) to retrieve final nutritional values and compare them with biomarkers and metabolites in blood.

Similarly, PA can be collected in a better way. The metabolic equivalent of task (MET) is a unit that measures how active a person is and roughly translates into 1 kcal/kg/hour, 1W/kg, or the energy required to sit down for an hour. In our questionnaires, PA is also self-reported and open to interpretation. Light activity includes walking and cycling, which vary from 2 to 6 METs. Medium activity includes recreational sports, such as light weightlifting (3.5 METs), tennis (5), basketball (8), football (10), jogging (11), or snow cleaning (4-8). Hard includes sports competitions, which again, vary too much for each type. Our categories have potential MET overlapping. METs have some limitations, and it is harder to calculate the exact value from person to person, but while it is also self-reported, it is a more objective measure of PA. This would also keep specific activities separated for better analysis. Alternatively, we could make use of accelerometers as has been reported in previous FF studies [83], but didn't have access to this data.

5 Conclusions

We saw that UVB radiation presents itself as the main influence of 25OHD levels in this population, even though low levels are present due to the Arctic geolocation. Among people not using solarium, those with greater numbers of friends with >50nmol/l tend to have higher levels of 25OHD themselves and vice versa, with an estimated probability of +7.25% per high vitamin D friend. FFQ seems to be a non-reliable tool for nutrition assessment and at the very least needs to be substituted with an ASA24s questionnaire; same with PA and METs.

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6 List of abbreviations

Acronym	Meaning
25OHD	25-hydroxycholecalciferol (Calcifediol)
4DFRs	4-d food records
ASA24s	Automated Self-Administered 24-h recalls
BMI	Body Mass Index
FF	Fit Futures
FFQs	food-frequency questionnaires
LC-MS/MS	High-pressure liquid chromatography-mass spectroscopy
M-BMs	memory-based dietary assessment methods
MET	metabolic equivalent of task
PA	Physical Activity
PTH	Parathyroid hormone
REK	Regional Committee of Medical and Health Research Ethics
UNN	University Hospital of North Norway
UVA	Ultraviolet A
UVB	Ultraviolet B
VDSP	Vitamin D Standardization Program

7 Declarations

7.1 Ethics approval and consent to participate

A declaration of consent was signed by each participant in FF1, participants younger than 16 years of age had to bring written consent from a parent or guardian. FF1 was approved by The Regional Committee of Medical and Health Research Ethics (REK) and the Norwegian Data Protection Authority. The present study was approved by REK North, reference 2011/1710 /REK Nord.

7.2 Consent for publication

Not applicable

7.3 Availability of data and materials

The Fit Futures data is not publicly available due to Norwegian privacy laws, but researchers can apply for access at <https://uit.no/research/fitfutures>

The analysis code is open source using the AGPLv3 license and it is available at our GIT repository (<https://github.com/uit-hdl/mimisbrunnr/>)

Our GIT repository also contains all results displayed here. Formats include Latex, CSV, and HTML for all tables, and PNG and PDF for all images. To avoid visual cluttering, some p-values displayed here are in GP Prism 5.04/d format (asterisks instead of numbers). The raw results contain all tables with both GP Prism format and the numerical format.

7.4 Competing interests

All authors state no conflict of interest.

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7.5 Funding

The “Population Studies in the North” (BiN) group at “UiT: The Arctic University of Norway” funded this study. The funders had no role in study design, data collection, analysis, interpretation, or decision to submit the manuscript for publication.

7.6 Authors contributions

RANC performed conceptualization, methodology, software, formal analysis, data curation, visualization, original draft, review, and editing of the paper. ASF and LAB performed review and editing, supervision, project administration, and funding acquisition. CSN participated in the conceptualization, review and editing, funding acquisition, and project administration. AMH collaborated with review editing and supervision.

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9 Supplementary materials

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10 High-schools information

10.1 Map overview

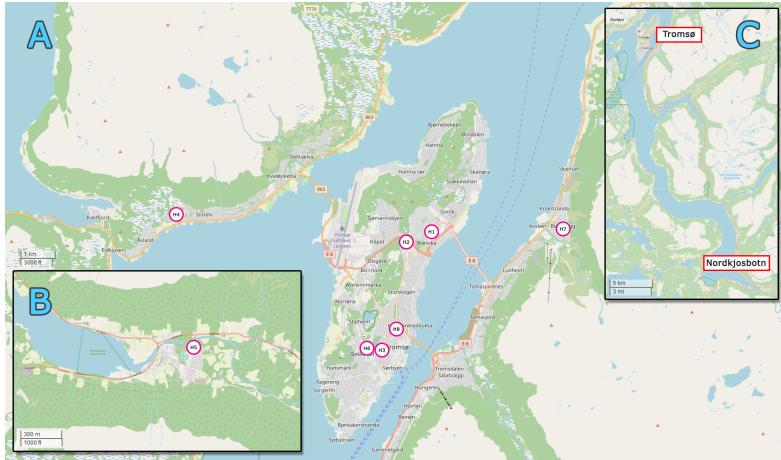


Figure 4: Overview map with the different high schools which were studied. Each high school location is highlighted with a circle with the ID of the school in the center. Area "A" is the view of the Tromsø area, schools H1 to H4 and H6 to H8 are located here. Area "B" is the view of Nordkjosbotn where H5 is located. Area "C" shows the distance and scale between A and B.

10.2 High-schools summary table

Table 3: Information with the school names, study program, the total number of students in FF1, astronomical season, and whether a significant part of the student's samples was taken during the polar night.

ID	Name	Studies program	FF1 Students	Extraction	Polar night
H1	Breivika videregående skole	Vocational	207	Autumn	No
H2	Brevang videregående skole	Vocational and General	142	Autumn	Yes
H3	Kongsbakken videregående skole	Vocational and General	168	Winter	No
H4	Kvaløya videregående skole	Vocational and General	98	Spring	No
H5	Nordkjosbotn videregående skole	Vocational and General	85	Spring	No
H6	Norges Toppidrettsgymnas Tromsø	Sports	26	Spring	No
H7	Tromsdalen videregående skole	Sports and General	192	Winter	Yes
H8	Tromsø maritime skole	Vocational	120	Winter	Yes

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10.3 High-schools dates of blood extraction

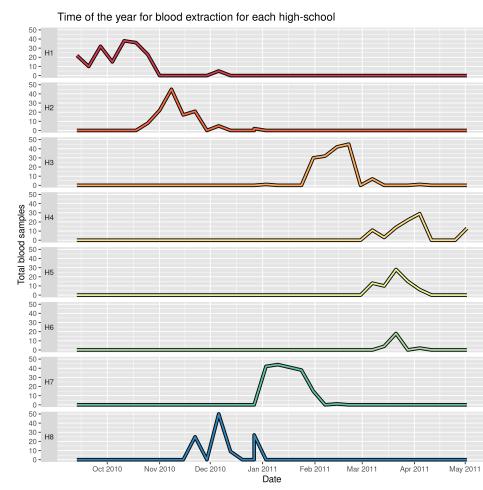


Figure 5: Total blood extractions per high school across time of the year for each high school.

11 Networks information

11.1 All graphs

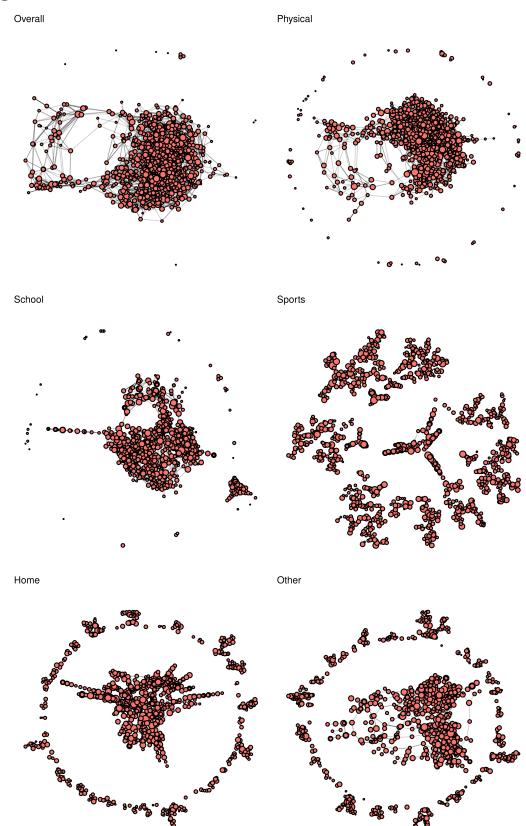


Figure 6: Overview of all friendship networks. The figure is reproduced from "Social network analysis of *Staphylococcus aureus* carriage in a general youth population" with permissions. DOI: <https://doi.org/10.1016/j.ijid.2022.08.018>

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11.2 Network relevance overview

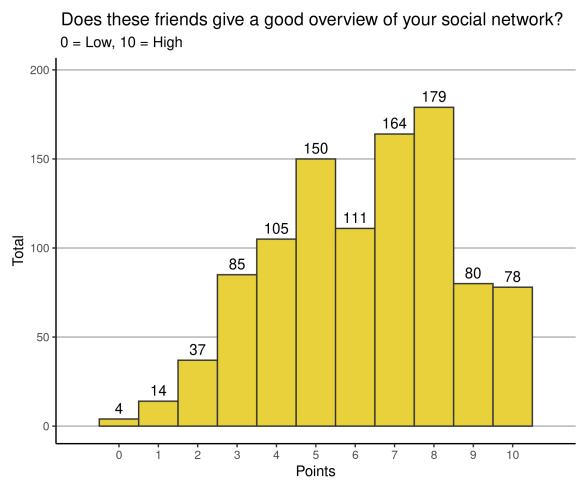


Figure 7: Histogram with how good is the self-reported network (0 - 10, x-axis) by each student (y-axis). The figure is reproduced from "Social network analysis of *Staphylococcus aureus* carriage in a general youth population" with permissions. DOI: <https://doi.org/10.1016/j.ijid.2022.08.018>

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11.3 Network relevance by high school

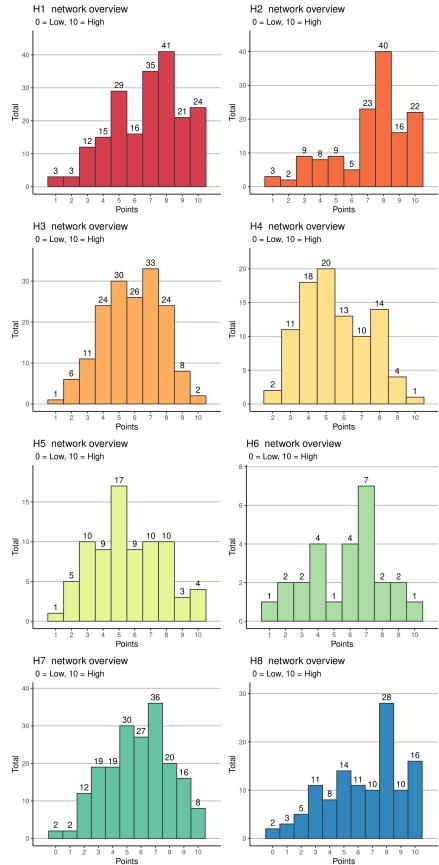


Figure 8: For each of the high schools (H1 to H8), histogram with how good is the self-reported network (0 - 10, x-axis) by each student (y-axis)

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11.4 Network relevance table

Table 4: Highschools and friendship overview. The first row represents all high schools combined. H1 to H8 rows represent each high school separately. Homophily represents how many students of this school form friendships with a student of the same school. Frequency is the relative frequency of students in each high school. Significance is the p-value of a two-sided binomial test of relationships within the same high school, total relationships, and relative frequency of students in each high school. Average and Median are the values of how good is the self-reported network (0 - 10) by each student in each high school.

High School	Homophily	Frequency	Significance	Average	Median
All	0.87			6.22	6
H1	0.76	0.2	****	6.77	7
H2	0.78	0.14	****	7.2	8
H3	0.76	0.16	****	5.84	6
H4	0.77	0.09	****	5.54	5
H5	0.96	0.08	****	5.55	5
H6	0.76	0.03	****	5.73	6
H7	0.79	0.18	****	5.8	6
H8	0.72	0.12	****	6.42	7

11.5 Non-solarium networks by high school

Non solarium relationships in Highschool 1
Fruchterman - Reingold layout with node size proportional to 25OHD levels

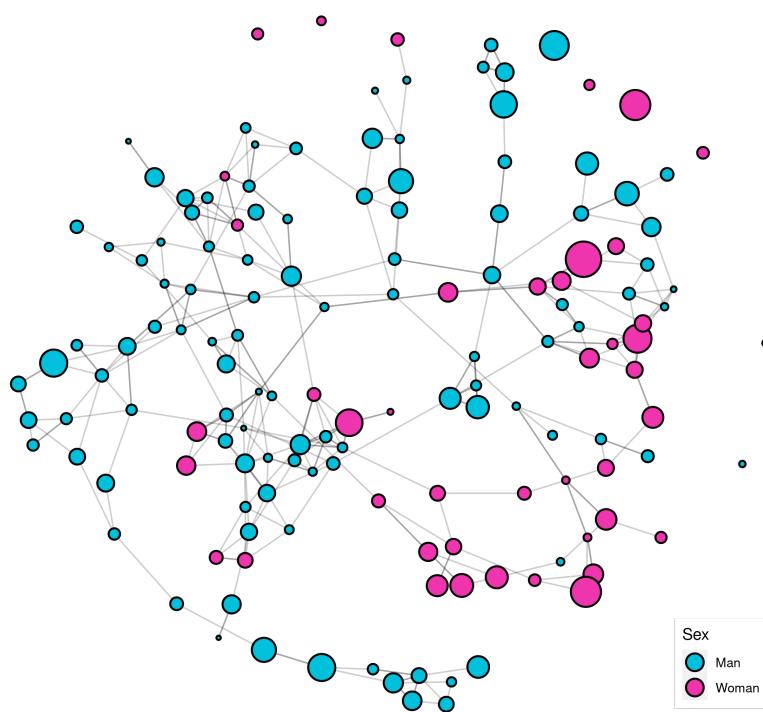


Figure 9: Relationships in H1 for non-solarium users highlighted by sex. Node size is proportional to the 25OHD level. Layout of the nodes using Fruchterman - Reingold. A total of 150 students and 255 undirected relationships are displayed.

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Non solarium relationships in Highschool 2
Fruchterman - Reingold layout with node size proportional to 25OHD levels

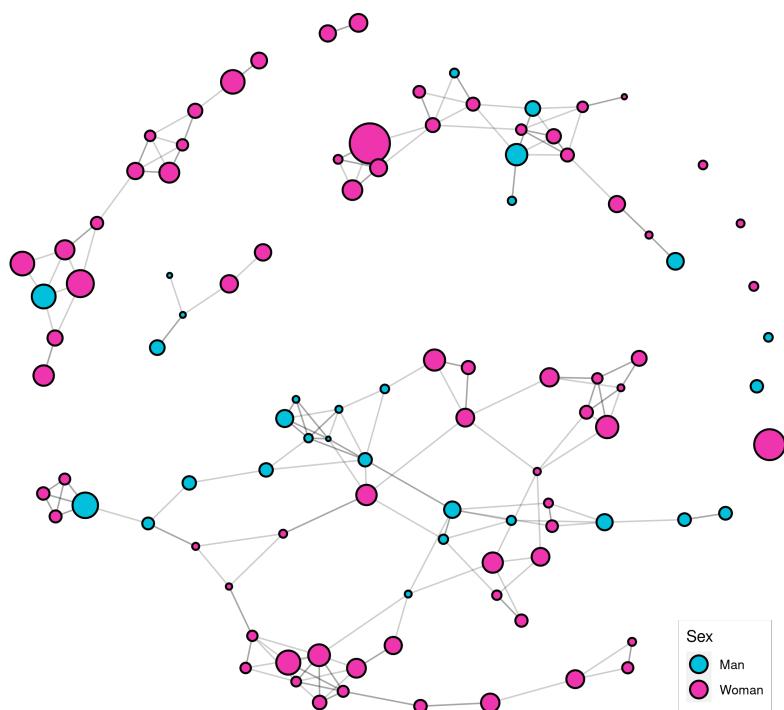


Figure 10: Relationships in H2 for non-solarium users highlighted by sex. Node size is proportional to the 25OHD level. Layout of the nodes using Fruchterman - Reingold. A total of 101 students and 157 undirected relationships are displayed.

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Non solarium relationships in Highschool 3
Fruchterman - Reingold layout with node size proportional to 25OHD levels

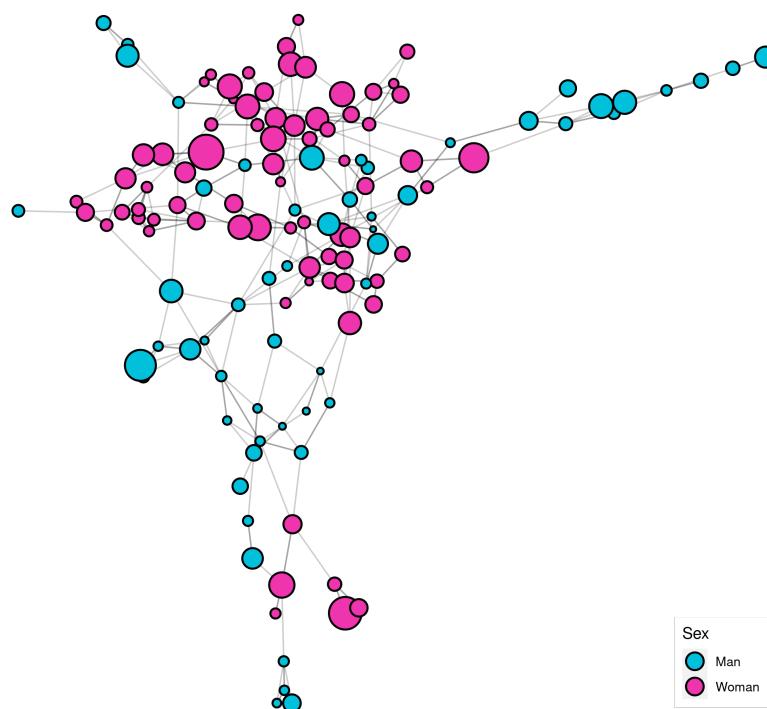


Figure 11: Relationships in H3 for non-solarium users highlighted by sex. Node size is proportional to the 25OHD level. Layout of the nodes using Fruchterman - Reingold. A total of 129 students and 247 undirected relationships are displayed.

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Non solarium relationships in Highschool 4
Fruchterman - Reingold layout with node size proportional to 25OHD levels

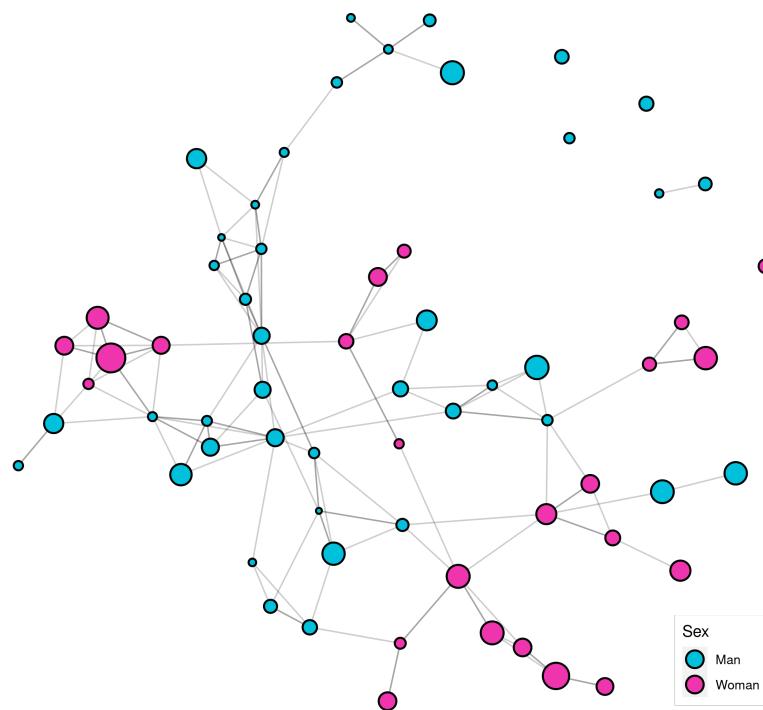


Figure 12: Relationships in H4 for non-solarium users highlighted by sex. Node size is proportional to the 25OHD level. Layout of the nodes using Fruchterman - Reingold. A total of 65 students and 110 undirected relationships are displayed.

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Non solarium relationships in Highschool 5
Fruchterman - Reingold layout with node size proportional to 25OHD levels

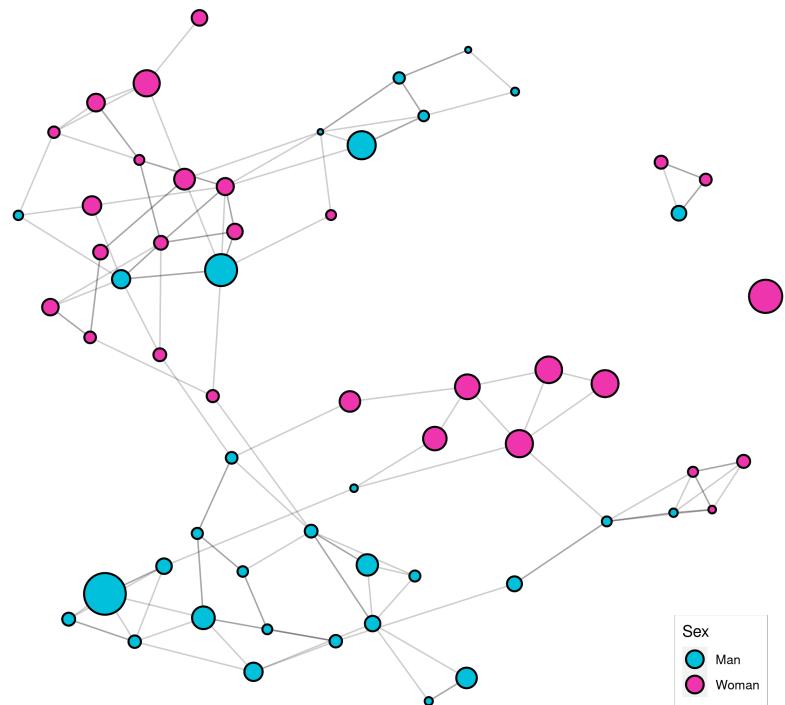


Figure 13: Relationships in H5 for non-solarium users highlighted by sex. Node size is proportional to the 25OHD level. Layout of the nodes using Fruchterman - Reingold. A total of 59 students and 102 undirected relationships are displayed.

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Non solarium relationships in Highschool 6
Fruchterman - Reingold layout with node size proportional to 25OHD levels

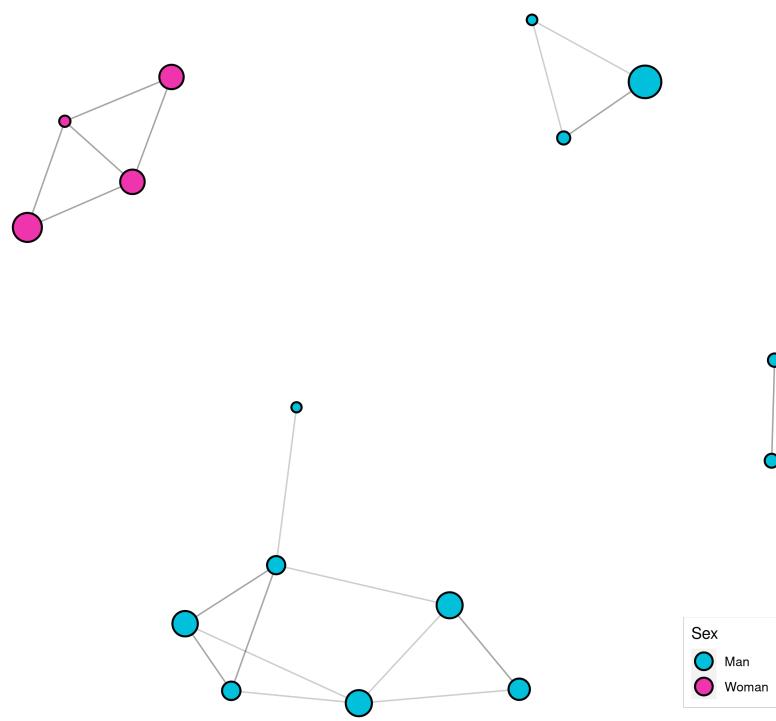


Figure 14: Relationships in H7 for non-solarium users highlighted by sex. Node size is proportional to the 25OHD level. Layout of the nodes using Fruchterman - Reingold. A total of 16 students and 19 undirected relationships are displayed.

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Non solarium relationships in Highschool 7
Fruchterman - Reingold layout with node size proportional to 25OHD levels

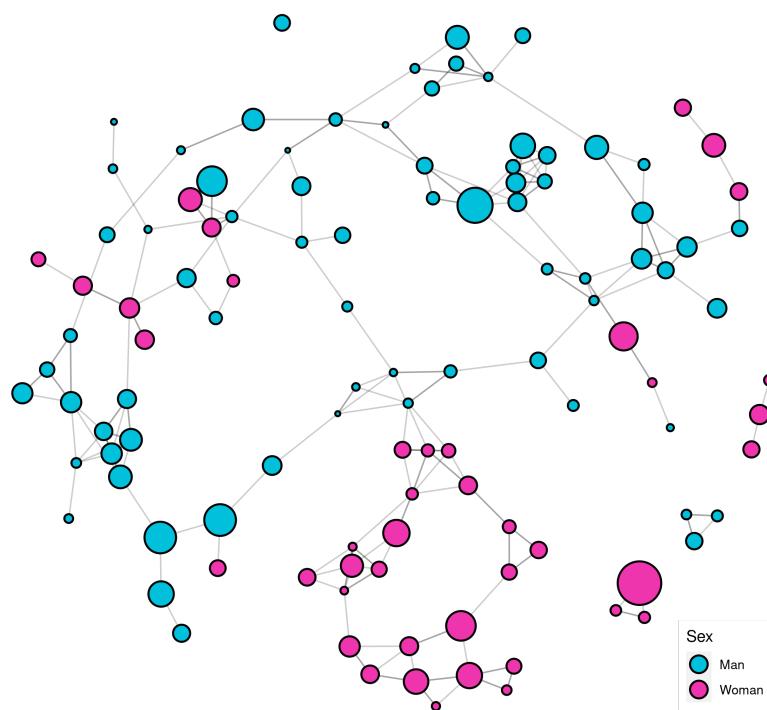


Figure 15: Relationships in H7 for non-solarium users highlighted by sex. Node size is proportional to the 25OHD level. Layout of the nodes using Fruchterman - Reingold. A total of 113 students and 180 undirected relationships are displayed.

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Non solarium relationships in Highschool 8
Fruchterman - Reingold layout with node size proportional to 25OHD levels

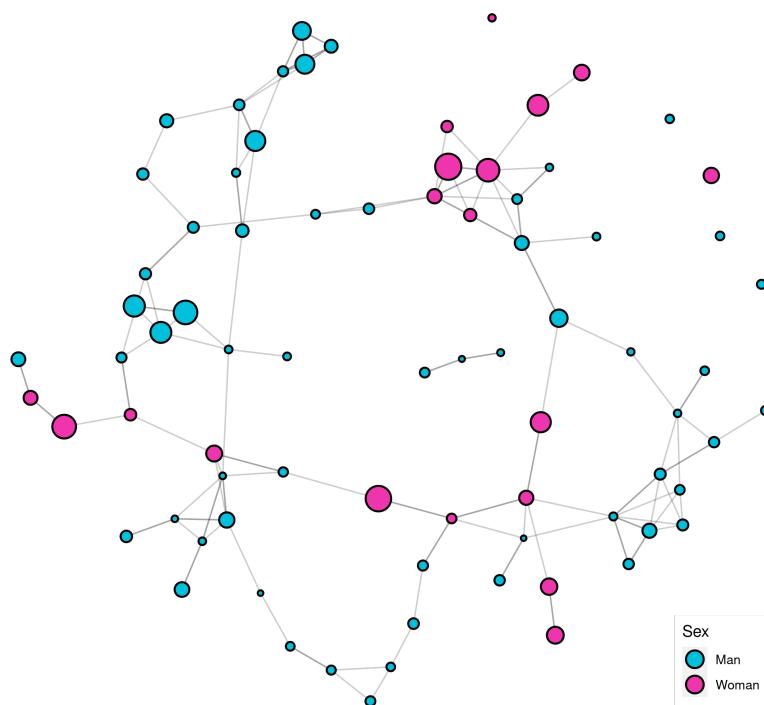


Figure 16: Relationships in H8 for non-solarium users highlighted by sex. Node size is proportional to the 25OHD level. Layout of the nodes using Fruchterman - Reingold. A total of 78 students and 112 undirected relationships are displayed.

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12 Other social influences

12.1 Non-solarium simulations by high school

Table 5: Simulations performed for each high school independently for non-solarium users.

Highschool	Relationships		Simulations statistics							P-value
	Total	Equal	MIN	Q1	Median	Average	Q3	MAX	SD	
H1	341	223	151	169	175	177.16	186	211	12.45	***
H2	221	137	92	109	116.5	116.2	123	154	10.26	*
H3	348	212	156	170	181	180.99	189	227	13.88	*
H4	153	101	57	74	81	81.24	88	104	9.75	*
H5	135	88	47	65	71	70.22	76	95	8.35	*
H6	30	20	9	13	16	15.96	19	23	3.42	ns
H7	251	141	102	123	132	131.05	138	159	10.52	ns
H8	152	114	63	72	78	78.46	85	98	8.28	****

12.2 25OHD and Friends' average 25OHD by high school

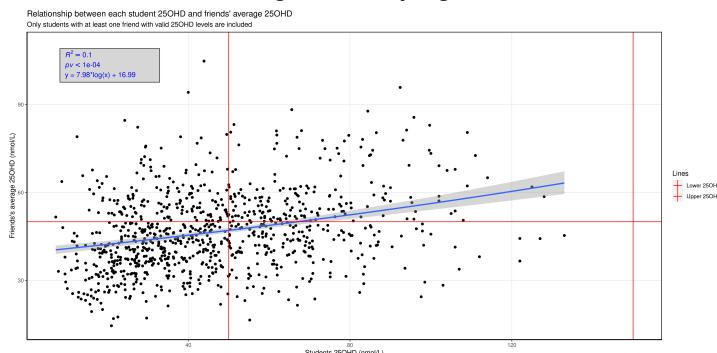


Figure 17: Relationship between each student 25OHD levels (X-axis) in comparison with the students' friends average 25OHD levels (Y-axis). Only students with a valid 25OHD value with at least one friend who also has a valid 25OHD value are included (n=930)

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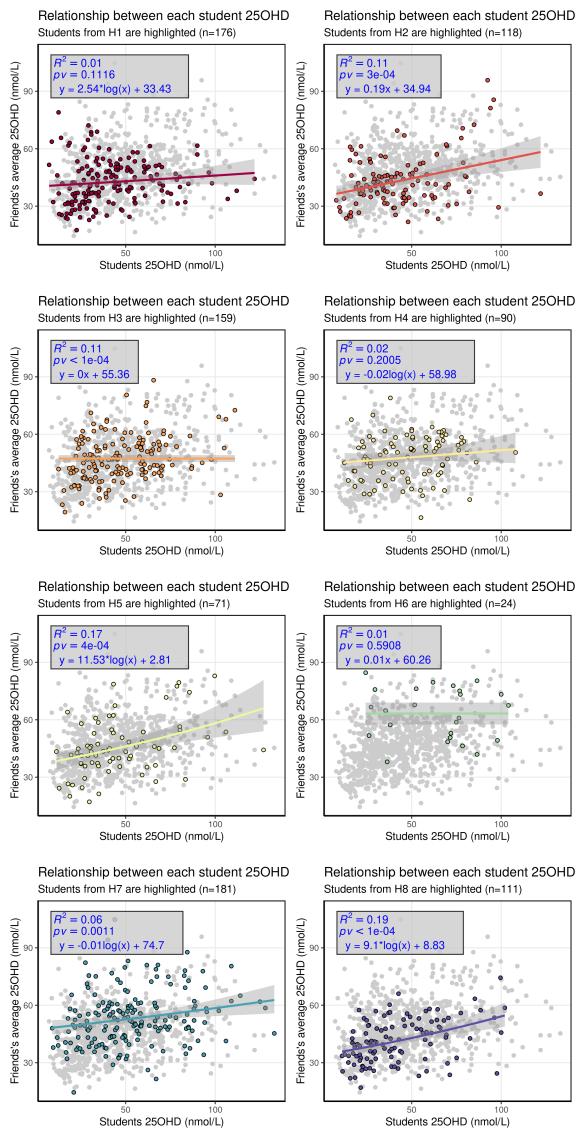


Figure 18: Relationship between each student 25OHD levels in comparison with the students' friends average 25OHD levels, for each high school. Students from other high schools are grayed out.

13 Ethnicity

Table 6: Absolute frequency for each ethnicity sorted by frequency

Modality	Count	Relative	Cumulative
Norwegian	900	0.867	0.867
Norwegian-Sami	27	0.026	0.893
Didn't Answer	20	0.019	0.912
Norwegian-Kven	10	0.01	0.922
Sami	7	0.007	0.929
Norwegian-Swedish	7	0.007	0.935
Russian	4	0.004	0.939
Norwegian-Sami-Kven	4	0.004	0.943
African	3	0.003	0.946
Afghan	3	0.003	0.949
Swedish	3	0.003	0.952
Norwegian-Somalian	3	0.003	0.955
Norwegian-Spanish	3	0.003	0.958
Norwegian-Danish	3	0.003	0.961
Other	2	0.002	0.962
Eritrean	2	0.002	0.964
Thai	2	0.002	0.966
German	2	0.002	0.968
Polish	2	0.002	0.97
Kven	2	0.002	0.972
Norwegian-Russian	2	0.002	0.974
Canadian	1	0.001	0.975
Tamil	1	0.001	0.976
Palestinian	1	0.001	0.977
Italian	1	0.001	0.978
Bulgarian	1	0.001	0.979
Belgian	1	0.001	0.98
Dutch	1	0.001	0.981
Norwegian-Other	1	0.001	0.982
Norwegian-Colombian	1	0.001	0.983
Norwegian-Brasilian	1	0.001	0.984
Norwegian-Canadian	1	0.001	0.985
Norwegian-Ghanaian	1	0.001	0.986
Norwegian-Gambian	1	0.001	0.987
Norwegian-African	1	0.001	0.987
Norwegian-Philipine	1	0.001	0.988
Norwegian-Tamil	1	0.001	0.989
Norwegian-Thai	1	0.001	0.99
Norwegian-Chinese	1	0.001	0.991
Norwegian-Turquish	1	0.001	0.992
Norwegian-Portuguese	1	0.001	0.993
Norwegian-Italian	1	0.001	0.994
Norwegian-Belgian	1	0.001	0.995
Norwegian-German	1	0.001	0.996
Norwegian-Finnish	1	0.001	0.997
Norwegian-Swedish-Dutch	1	0.001	0.998
Norwegian-Sami-Icelandic	1	0.001	0.999
Norwegian-Sami-Swedish	1	0.001	1

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Table 7: *Chi-square test skin group and high-school*

0.5	Fair	Dark	Total	Freq
H1	190/192	7/4	197	0.19
H2	135/136	5/3	140	0.14
H3	164/163	3/3	167	0.16
H4	95/94	2/2	97	0.1
H5	81/79	0/1	81	0.08
H6	26/25	0/0	26	0.03
H7	188/186	3/4	191	0.19
H8	117/116	2/2	119	0.12
Total	996	22	1018	
Freq	0.98	0.02		1

14 Non solarium distributions by high schools

14.1 Sex

Table 8: *Xi² table with respect to sex and high school*

7e-13	Man	Woman	Total	Freq
H1	107/85 ++	43/64 —	150	0.21
H2	29/57 —	72/43 +++++	101	0.14
H3	56/73 —	73/55 ++	129	0.18
H4	41/37	24/27	65	0.09
H5	31/33	28/25	59	0.08
H6	12/9 4/6		16	0.02
H7	71/64	42/48	113	0.16
H8	59/44 ++	19/33 —	78	0.11
Total	406	305	711	
Freq	0.57	0.43		1

14.2 BMI

Table 9: *Xi² table with respect to BMI and high school*

9e-04	Underweight	Healthy	Overweight	Obese	Total	Freq
H1	16/16	91/100	26/20	16/11	149	0.21
H2	14/11	57/67	16/13	13/7 +	100	0.14
H3	13/14	96/86	15/17	5/10 -	129	0.18
H4	12/7 +	39/43	9/8	5/5	65	0.09
H5	4/6	40/39	6/8	9/4 ++	59	0.08
H6	0/1	16/10	0/2	0/1	16	0.02
H7	15/12	88/75	8/15	— 2/8	113	0.16
H8	6/8	49/52	17/10	++ 6/6	78	0.11
Total	80	476	97	56	709	
Freq	0.11	0.67	0.14	0.08		1

14.3 Alcohol

Table 10: *Xi² table with respect to alcohol and high school for non-solarium users*

0.001	Never	Once per month or less	Twice or more per month	Total	Freq
H1	44/45	60/56	37/38	141	0.2
H2	36/32	38/40	26/27	100	0.14
H3	40/41	61/52	28/35	129	0.19
H4	25/20	23/25	16/17	64	0.09
H5	17/18	17/22	23/15 +	57	0.08
H6	11/5 ++	5/6	0/4 -	16	0.02
H7	38/36	48/45	27/30	113	0.16
H8	14/24 —	29/31	34/21 +++	77	0.11
Total	225	281	191	697	
Freq	0.32	0.4	0.27		1

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14.4 Smoke

Table 11: *Xi2 table with respect to smoke and high school for non-solarium users*

8e-06	Never	Sometimes	Daily	Total	Freq
H1	102/112	31/22	++ 8/6	141	0.2
H2	76/79	15/15	8/4 +	99	0.14
H3	111/103	18/20	0/5 —	129	0.19
H4	59/51	4/10	- 1/2	64	0.09
H5	37/45	15/8	+ 5/2	57	0.08
H6	16/12	0/2	0/0	16	0.02
H7	102/90	10/17	- 1/5	113	0.16
H8	54/62	16/12	8/3 ++	78	0.11
Total	557	109	31	697	
Freq	0.8	0.16	0.04		1

14.5 Snuff

Table 12: *Xi2 table with respect to snuff and high school for non-solarium users*

3e-07	Never	Sometimes	Daily	Total	Freq
H1	85/96	15/15	42/30 ++	142	0.2
H2	63/67	12/10	24/21	99	0.14
H3	99/87	15/13	15/27 —	129	0.19
H4	47/43	3/6	14/13	64	0.09
H5	38/38	6/6	13/12	57	0.08
H6	15/10	1/1	0/3 -	16	0.02
H7	92/76 +	12/11	9/24 —	113	0.16
H8	34/52 —	10/8	33/16 ++++	77	0.11
Total	473	74	150	697	
Freq	0.68	0.11	0.22		1

14.6 Sports

Table 13: *Xi² table with respect to sport and high school for non-solarium users*

9e-34	None	Light	Medium	Hard	Total	Freq
H1	44/36	63/47	++	30/34	5/23	—
H2	38/25	++	40/33	14/24	—	8/16
H3	24/33	-	44/42	42/31	++	19/21
H4	16/16		14/21	21/15		13/10
H5	15/14		19/18	21/13	+	2/9
H6	0/4	-	0/5	—	0/3	—
H7	12/29	—	22/37	—	33/27	46/18
H8	32/20	+++	30/25	10/19	—	6/12
Total	181		232	171	115	699
Freq	0.26		0.33	0.24	0.16	1

14.7 Sunbathing

Table 14: *Xi-square test for sunbathing and high school for non-solarium users.*

4e-07	Yes	No	Total	Freq
H1	25/10	++++	124/138	149
H2	5/7		96/93	101
H3	5/9		124/119	129
H4	1/4	-	64/60	65
H5	2/4		57/54	59
H6	5/1	+++	11/14	16
H7	6/8		107/104	113
H8	3/5		74/71	77
Total	52		657	709
Freq	0.07		0.93	1

15 Other figures

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15.1 PTH predictors

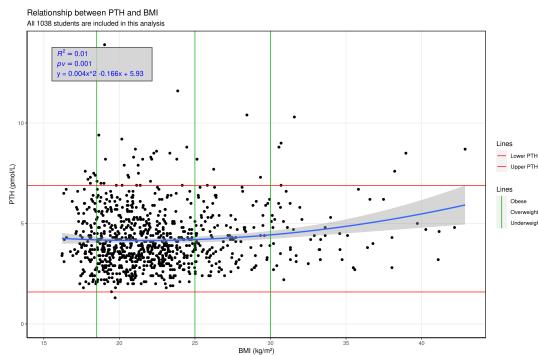


Figure 19: Relationship between PTH and BMI. All the students are included in this analysis. Vertical lines represent the threshold between BMI categories. Horizontal lines represent the healthy boundaries of PTH levels.

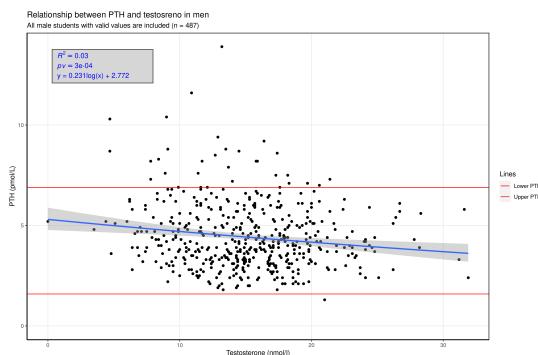


Figure 20: Relationship between PTH and testosterone in men. All the students are included in this analysis. Horizontal lines represent the healthy boundaries of PTH levels.

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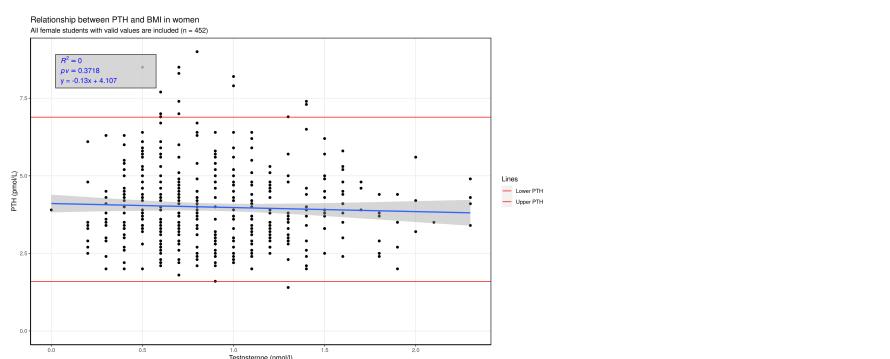


Figure 21: Relationship between PTH and testosterone in women. All the students are included in this analysis. Horizontal lines represent the healthy boundaries of PTH levels.

A.3 Paper C



An introduction to network analysis for studies of medication use

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ABSTRACT

Background: Network Analysis (NA) is a method that has been used in various disciplines such as Social sciences and Ecology for decades. So far, NA has not been used extensively in studies of medication use. Only a handful of papers have used NA in Drug Prescription Networks (DPN). We provide an introduction to NA terminology alongside a guide to creating and extracting results from the medication networks.

Objective: To introduce the readers to NA as a tool to study medication use by demonstrating how to apply different NA measures on 3 generated medication networks.

Methods: We used the Norwegian Prescription Database (NorPD) to create a network that describes the co-medication in elderly persons in Norway on January 1, 2013. We used the Norwegian Electronic Prescription Support System (FEST) to create another network of severe drug-drug interactions (DDIs). Lastly, we created a network combining the two networks to show the actual use of drugs with severe DDIs. We used these networks to elucidate how to apply and interpret different network measures in medication networks.

Results: Interactive network graphs are made available online, Stata and R syntaxes are provided. Various useful network measures for medication networks were applied such as network topological features, modularity analysis and centrality measures. Edge lists data used to generate the networks are openly available for readers in an open data repository to explore and use.

Conclusion: We believe that NA can be a useful tool in medication use studies. We have provided information and hopefully inspiration for other researchers to use NA in their own projects. While network analyses are useful for exploring and discovering structures in medication use studies, it also has limitations. It can be challenging to interpret and it is not suitable for hypothesis testing.

Introduction

Studies in social pharmacy and pharmacoepidemiology often utilize highly complex data and require the use of sophisticated methods to discern important patterns. Data used for quantitative studies in social pharmacy and pharmacoepidemiology can be described as attribute data and relational data. Attribute data includes the characteristics of the studied objects (e.g. sex, age, medication use, sociodemographic information, etc.) while relational data contains the various relationships between subjects. The suitable way of studying attributes data is quantitative analyses, whereas, for relational data, Network Analysis (NA) is the appropriate approach.¹ The subjects studied in network analyses can take many different forms.

A network can be described as a graph that shows the interconnections between a set of actors. Each actor is represented by a node and each connection between these nodes is represented by an

edge.² NA is a mathematical approach to study the relationships among nodes.³ The mathematical background of NA are summarized elsewhere.^{4,5}

Network Analysis has its roots in many research disciplines.⁶ Network analysis is used, among others, in social studies,⁷ ecological studies,⁸ genetics⁹ and systems pharmacology.¹⁰

As seen in Fig. 1, a network can be undirected (a and b) or directed (c and d). In a directed network, arrows show the direction of the relationship between nodes. In an undirected network, the relationship does not have a specific direction. The network edges can be weighted (b and d) or unweighted (a and c). In an unweighted network, the two nodes either have a relationship or not, while a weighed network considers the strength of the relationship.

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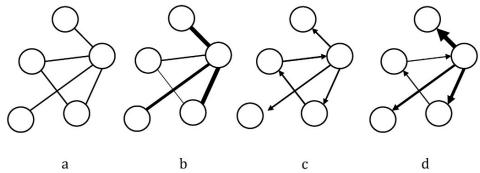


Fig. 1. Different types of networks, a) undirected and unweighted network, b) undirected and weighted network, c) directed and unweighted, and d) directed and weighted.

Use of Network Analysis in public health

Transmission networks have been used to examine the risk of disease transmission by investigating the relations between the infected people and healthy ones.^{11–13} Another form of transmission is the transmission of information. NA has been used to visualize the dissemination of public health information to different organizations and consumers. Some network characteristics reveal the pattern and the main actors contributing the most to information spread. Simulated networks can be used to suggest how to accelerate information spread.¹⁴ An example of this type of networks, the diffusion of information among physicians regarding a new drug. The study showed that more socially integrated physicians introduced the drug months before corresponding isolated physicians. NA was also used to study how health workers' professional and personal behavior impact health services.^{16,17}

Drug prescription network (DPN)

Pharmacoepidemiological studies of medications that are prescribed or dispensed is a relatively new application of NA. To our knowledge, Cavallo et al. were the first to study a drug prescription network in 2013. They used medications as the nodes and the number of patients being prescribed these medications as weighted edges. They aimed mainly at describing the topology of the co-prescription network to demonstrate which drug classes are most co-prescribed. They also compared the male/female networks and networks from different age strata and found that women in general were co-prescribed more drug classes.¹⁸

Bazzoni et al. were the first to use the term Drug Prescription Networks (DPN) in their paper published in 2015. They concluded that the DPNs are dense, highly clustered, modular and assortative. In this specific study, density reflected frequent co-prescribing. Modularity suggested that the network could be subdivided into clusters. The study also showed that it is possible to highlight spatial and temporal changes by

comparing different networks.¹⁹

Network Analysis terminology

We organized the key measures that are useful in studies of medication use under 4 main categories: (1) Topology analysis (2) Modularity analysis (3) Network comparison (4) Bipartite networks.²⁰ (Fig. 2).

1. Topology analysis

Network topological features refer to a group of characteristics, which either describe the network as a whole (network-level) or define individual actors of the network (node-level). There are many topological measures and each of them gives information about a specific network attribute, which then may warrant further investigation.

a. Global network description (network-level): A group of measures that describe the network as a whole.

- Number of nodes: the total number of drugs in the network. The network nodes can be grouped to show the number of drugs in each drug class. Different networks of different populations will have different distributions of drugs in the drug classes.
- Density: the density of a network is the number of actual edges divided by the total number of edges that would exist if all the nodes in the network were connected. This potential number can be calculated by the formula below where n is the number of nodes:

$$\frac{n \times (n - 1)}{2}$$

The network density can be useful in terms of comparison between different networks that describe the same type of drug-drug relation.

Assortativity: a network is assortative when the nodes that share a similar trait tend to connect. This trait can be many characteristics such as the nodes' degree. In this case, the assortativity means that nodes with a high number of edges tend to connect. Assortativity can be examined in terms of other common characteristics between the nodes as well. Assortativity coefficient is measured using Pearson correlation coefficient. Assortativity coefficient is scaled between -1 and 1, where 1 is most assortative.²¹

b. Node-level measures

Node-level measures describe the features of the different nodes across the network.

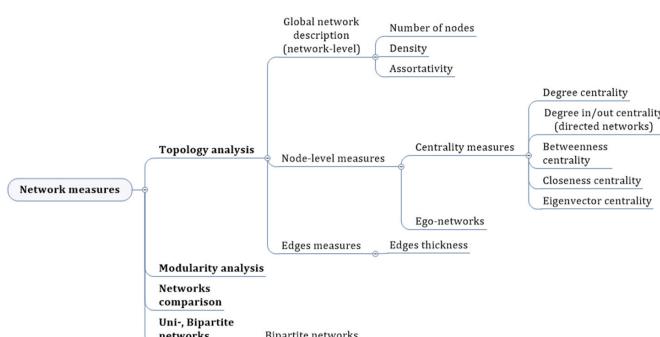


Fig. 2. Summarizing some of the Network Analysis measures that can be useful in the studies of medication use.

Centrality measures

Centrality measures indicate the importance of the network nodes by assigning a score to each of them. There are many different centrality measures and each of them can be used to describe a specific type of importance. By comparing the different centrality measures of a node, we can understand the different ways a node is influential to the network. This paper will discuss 4 of the most common types of centrality measures: degree, betweenness, closeness, and eigenvector centrality. The mathematical explanations of these measures are mentioned here.^{22,23}

Degree centrality

Degree centrality is the number of edges that are connected to a node. A higher score indicates that the node is connected to many other nodes. Node A in Fig. 3 has a degree score of 4. In a directed network, the degree is split into In-degree, which is the number of edges that direct to a node and Out-degree, which is the number of edges that originate from the node. In- and Out-degrees will therefore show the directions of relationships in a directed network. In Fig. 3, nodes C and D have an in-degree score of 3, while nodes A and G have an out-degree score of 3.

Betweenness centrality

The betweenness centrality of a node indicates how many times this node was used to connect two other nodes by the shortest possible path. Increasing the number of shortest paths will increase the betweenness centrality score.²² In Fig. 3, node A has the highest betweenness centrality score of 1.5.

Closeness centrality

It is a measure of the average distance between the node and all other nodes in the network. Nodes with the highest closeness score have the shortest distances to all other network nodes. The nodes A, B and F have the highest closeness centrality score of 1.

Eigenvector centrality

It is a measure of the importance of a node in a network based on the node's connections with other vital nodes. Relative scores are given to all nodes in the network based on the concept that connections to high-scored nodes give a higher score to the node than equal connections to

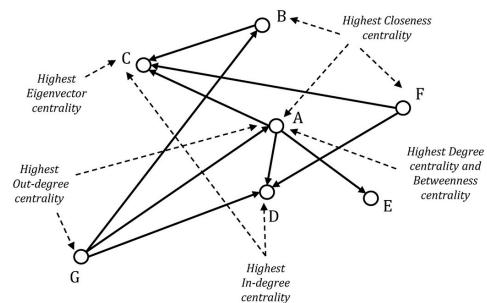


Fig. 3. Illustrating the different types of centrality. Node (A) represents the highest score of Degree and Betweenness centralities. The highest Eigenvector centrality score is assigned to the node (C). Nodes (A, B, F) have similar closeness Centrality. Nodes with the most in-degree edges are (C, D), while (A, G) have the most out-degree edges.

low-scored nodes. In other words, a high eigenvector score means that a node is connected to many nodes, which themselves are connected to important nodes in the network and have high scores of eigenvector centrality. This means that a node with a high eigenvector centrality score is not necessarily connected to the highest number of nodes in the network but is connected to the nodes with a high number of edges.²⁴ Node C in Fig. 3 has the highest eigenvector centrality score of 1. Assigning the centrality of each node in the network may lead us to visualize the network from a single specific important node perspective; this is called an *Ego-network* and it visualizes the part of the network that has the node of interest and the nodes that are directly connected to it.

c. Edge-level measures

Edge-thickness: in a weighted network, the edge-thickness represents a quantitative measure of the strength of the connection between two nodes. This representation is unique for NA and can be used to study many research questions. We will show an example where the number of users that co-medicated a pair of medications are used to represent the edge-thickness. In this context, thicker edges represent more frequently used pairs of medications.

2. Modularity analysis (Community detection)

One key feature of the network structure is its modularity. A module is a group of nodes that have many connections between each other and few(er) connections to the other nodes in the network.²⁵ There are many techniques of community detection including density-based, centrality-based, partition-based and hierarchical clustering techniques^{20,26,27}

3. Network comparison

It is possible to compare two or more networks to show the changes over time (temporal), between different areas (spatial), or between different groups of patients. These comparisons can be done by comparing the characteristics of the networks to highlight the differences in numbers and influences of the nodes. Another way to compare different networks is to subtract or divide the values of the edges between two networks. This will create edges representing the differences between the networks. By comparing many networks, dynamic graphs can be created showing the topological changes from a network to the next. Nodes will appear, disappear or change their locations as the dynamic graph moves through the different networks.²⁸

4. Bipartite networks

A network can be uni- or multipartite. We will only discuss uni- and bipartite networks. Unipartite networks have one set of nodes, while in bipartite networks the nodes belong to two disjointed sets (such as prescribers and patients). In a bipartite network, edges connect the nodes from different sets^{29,30} (Fig. 4).

The aim of this paper is to introduce the readers to NA as a tool to

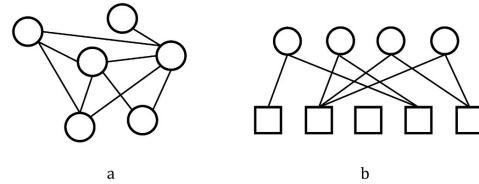


Fig. 4. (a) Unipartite network consisting of one type of nodes; (b) bipartite network consisting of two different types of nodes (circles and squares) in which the edges link between nodes from different types.

study medication use by demonstrating a practical real-life example of medication use in the elderly in Norway whenever it is possible, otherwise by giving an example from other studies.

Methods

We created a network of co-medication in elderly persons in Norway. We also created a network describing the severe drug-drug interactions (DDIs). Finally, we generated a network with the actual use of drugs with severe DDIs by combining the previous two networks.

Data sources

Co-medication network

The dataset used comes from the Norwegian Prescription Database (NorPD). It covers all dispensed prescriptions to elderly persons (≥ 65 years) in Norway between 2012 and 2014. The NorPD collects data from all pharmacies in Norway and covers all outpatient dispensing for the entire Norwegian population. Details on the NorPD are published elsewhere.³¹ In total, the dataset included 765,383 patients, 344,285 men (45%) and 421,098 women (55%) with 75 years as mean patient age. Edges in this network represent the number of patients who combined pairs of medications. In order to define the co-medication, we created treatment episodes using the Proportion of Days Covered (PDC) approach.³² We assumed that patients used one Defined Daily Dose (DDD)³³ per day and added 20% to each prescription duration to account for imperfect adherence. We also allowed a medication-free gap of 14 days before ending a treatment episode and starting another. This means that if the patient exceeds 14 days without the medication, the treatment episode for this medication ends and a new episode starts if the patient picks up a new prescription. Finally, co-medication was defined as the overlapping drug treatment episodes at the index date, January 1, 2013.

For each pair of nodes (drugs), we summed up the number of co-medication occurrences (i.e. number of patients combining these two drugs) to create a weighted and undirected network.

We excluded the medications that have no defined DDD such as the medications for topical use, vaccines, and ophthalmologicals. In total, we excluded 357 medications (217 local and 140 systematic drugs). The co-medication network is shown here: <https://mohsenaskar.github.io/co-medication/network/>. The network is searchable by substance name. Clicking on any node shows the ego-network of this node as well as some network measures.

Severe drug interactions network

To create this network, we used a dataset derived from the Norwegian Electronic Prescription Support System (FEST). FEST is a national information service that provides common pharmaceutical data to the IT-systems that are involved in the drug prescribing process including systems used by physicians, hospitals and pharmacies.³⁴ Drug-drug interactions is a part of the FEST database. In FEST, the DDIs are divided into 3 categories; interactions that should be avoided (i.e. severe), interactions where precautions should be taken and interactions that do not require any action. Only severe DDIs were included in the study. There were 57,151 unique severe interactions. The edges in this network represent the presence of a severe interaction between the two nodes.

The network is undirected and unweighted. The severe DDIs network is shown here: <https://mohsenaskar.github.io/DDI/network/>

Combining co-medication and DDIs networks

Both DDI and co-medication network has drugs as nodes. When combining the two networks only edges that exists in both networks are included (only edges with any users combining the medications and where there is a severe DDI). The number of users for each edge from the co-medication network becomes the weight of the edges in the combined network.

This network is shown here: <https://mohsenaskar.github.io/DDI-i-n-co-medication-network/network/>

Preparing the data to create a network

The data from the NorPD contains attributable data including a patient identity number, sex, year of birth, and data about each individual dispensed drug. To create a network, this data needed to be reshaped. The first step was to create a file with only medications that were used on the index date. Secondly, the file was aggregated such that an edge list was created. The edge list contains 2 variables defining the pairs of drugs and one variable with the number of users co-medicating with each pair of drugs. This edge list can be used by various software as described below. The process of data preparation is summed up in Fig. 5 and the edge list is openly available at the UiT The Arctic University of Norway open data repository here: <https://dataverse.no/dataset.xhtml?persistentId=doi:10.18710/1OUTYI>. The Stata syntax for creating the edge list is supplied in supplementary 2.

Software to use for network analysis

There are many available tools to use for NA. We will focus on how to use the *nwcommands* suite of commands that can be downloaded into *Stata* and the *igraph* package in *R* as well as visualization in *Gephi*. Other packages like “*igraph*” or “*NetworkX*” for *Python* are popular as well. All these packages can be used for visualizing and computing different network measures with differences in their integrated features and performance.^{35,36}

Using Stata (*nwcommands*, *nwANND*)

Using the edge list, *nwcommands* will create an adjacency matrix.³⁷ The adjacency matrix is a square matrix that contains the relationships between every pair of nodes in the network. The adjacency matrix can be saved as *Pajek* format that can be later imported and used by *Gephi*. In addition, *nwcommands* can display some network measures on both the network and node-level. *NwANND* is used for calculating the assortativity coefficient.³⁸ The syntax can be found in supplementary 2.

Using R (*igraph*)

Igraph (<https://igraph.org/>) is a library for creating and analyzing graphs. It is widely used by network researchers to analyze graphs and networks. It is currently available for *C*, *C++*, *Python*, *R* and *Mathematica*.

One of the strengths of *igraph* is that it can be programmed with a high-level programming language and still be very efficient when handling large networks. In our *R* context, *igraph* integrates well with the visualization package (*ggplot2*) via the *ggraph* library.

Igraph uses an edge list and can link it with attribute data for each node as well. An example code for network visualization using *igraph* and *ggraph*, is given in Supplementary 2.

Using gephi

Gephi (<https://gephi.org/users/>) is an open-source and free stand-alone software. The software can handle small to medium-sized networks (up to 150000 nodes). *Gephi* is user-friendly and requires no programming experience.³⁹ With many visualizing layouts and network measures, *Gephi* can provide a good starting point for the drug network study.³⁹ After importing the adjacency matrix to *Gephi*, we can process the network by applying different visualizing layouts, adding filters and colors. The structure of most drug networks can be complex and the unprocessed form of the network is often uninformative. By using different attributes (e.g. sex, modularity, etc.) the network can become more easily interpretable.²⁸

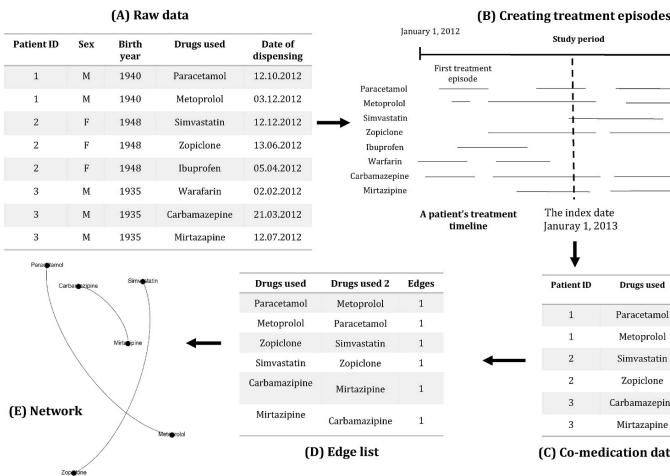


Fig. 5. Data preparation process. A) Raw clinical data in the long-form. B) Creating treatment episodes, a line indicates an episode. Gaps between lines indicate a medication-free period of more than 14 days. C) Data including only medications used at the index date D) Creating the edge list including 3 variables; two variables represent the nodes (Drug used, Drug used 2) and the third variable is the edge weight between the pair of nodes. E) Using the software to generate the network.

Results

We will present results from our networks using the same terms and order as in the introduction (Fig. 2). Table 1 provides the main topological features of the co-medication and the severe DDIs networks. The co-medication network is denser than the severe DDIs network, indicating that the drugs in the co-medication network are more connected. The assortativity coefficient shows that the co-medication network is non-assortative in terms of degree similarity, while the severe DDIs network is more assortative. Centrality measures in the co-medication network revealed that the same 5 drugs are the most central in all measures, while in the severe DDIs network; there is more variation in the top 5 drugs in each centrality measure. The results also showed that both networks are modular.

Fig. 6 shows that the majority of anatomical drug classes were assortative. This means that the drugs from the same anatomical group tend to be more co-prescribed. We also investigated the assortativity of the drugs on the pharmacological level (3rd level Anatomical Therapeutic Chemical classification) in supplementary 3.

Ego-networks as a measure can be seen by accessing the online networks we created and selecting individual nodes. The different network links can be found in the method section.

The top 10 edge weights for the severe DDIs in the co-medication network and co-medication only network are shown in Tables 2 and 3 respectively. We see in Table 2 that the number of patients using drugs causing severe DDIs are relatively low (less than 1000 users for all) while the most commonly co-medicated drugs seen in Table 3 is much higher with acetylsalicylic Acid (aspirin) and simvastatin having around 83000 users representing almost 11% of the population.

Modularity analysis

We found 4 modules in the co-medication network and 11 modules in the severe DDI network. For the co-medication network, there was one large community and 3 other smaller communities. Nervous and Respiratory system groups (N- and R-groups) drugs are just found in module 0, while Cardiac-, Alimentary-, Blood groups(C, A-, B- groups)

are common groups between modules 1 and 2, but with considering the number of users in each module we can locate in which module these ATC groups represent the most importance. Drugs used for diabetes, (A10) group, present only in module 2. The complete tables of modules are listed in supplementary 1. For the severe DDIs network, the modules found are shown below in Fig. 7.

Discussion

A Network visualizes the relationships of a dataset in one graph. This unique ability of data representation is combined with many measures that are helpful for many research disciplines. A starting point for generating any network is to select the nodes and define the edges. A precise definition of the edges allows the researcher to extract the correct information. NA is a well-suited approach to study complex systems. Although the approach has been widely used in many fields of research, only a few studies studied the drug-relations in a network.^{18,19}

Our results show that many network outcomes can be useful in the studies of medication use. Moreover, some results are unique measures that only NA can perform such as edge measure and modules detection. Employing centrality measures in the drug study introduce an opportunity to observe the influence of the different drugs in the drug-network. Determining this influence can be useful for clinicians and decision-makers.

After generating a network, some topological features have to be reported first to get a general idea about the network content and its basic characteristics. Network-level measures such as assortativity and density reveal many clues for further investigation. Centrality measures show how influential each node is in the network. It is possible to have high centrality of one type and a low of another for the same node.⁸ In order to study the importance of the nodes, it is necessary to use more than one measure of centrality. Recent studies suggest using centrality measures as an alternative approach for variables selection. Lutz et al. used the centrality measures to identify 4 additional variables contributing to the predicting of treatment dropout in patients with anxiety disorders.⁴⁰ Valenzuela et al. described a methodology based on degree and centrality measures to obtain the most representative variables for

Table 1
The topological measures of co-medication and severe DDIs networks.

Outcome	Co-medication network	DDIs network	Indicates
1. Topology analysis			
a) Network-level measures			
Number of nodes	762	1699	Number of drugs present in the network.
Number of edges	75052	57151	Number of connections between the network nodes
Density	0.26	0.04	The extent of connections between the network's nodes
Average degree	99	34	The average number of connections that each node has.
Assortativity coefficient	-0.26	0.4	To what extent nodes with higher degree tends to correlate.
b) Node-level measures			
<i>Centrality measures</i>			
Nodes with the highest Degree centrality scores	Acetylsalicylic acid Simvastatin Zopiclone Paracetamol Metoprolol	Typhoid vaccine Erythromycin Prilkerium Clarithromycin Moxifloxacin	Combining these centrality measures can be used to assign the importance of each drug to the network.
Nodes with the highest Betweenness centrality scores	Acetylsalicylic acid Simvastatin Zopiclone Paracetamol	Typhoid vaccine Padelipofin Hyperici herba (St John's-wort) Tuberculosis vaccine Ginkgo leaves	
Nodes with the highest Closeness centrality scores	Acetylsalicylic acid Simvastatin Zopiclone Paracetamol Metoprolol	Bromelains Telbivudine Peg interferon alfa-2a Diazepam Oxazepam	
Nodes with highest Eigenvector centrality scores	Acetylsalicylic acid Simvastatin Zopiclone Metoprolol Paracetamol	Typhoid vaccine Erythromycin Clarithromycin Chloramphenicol Moxifloxacin	
c) Edge-level measures			
Average path length	1.77	3.09	Average shortest path between two nodes.
Thickest edge weight	82948	1	For the weighted co-medication network the number reflects the highest number of patients co-medication. This highlights clinically important combinations.
Edges range	1–82948	0–1	
2. Modularity			
Modularity	0.088	0.54	Indicates presence of modules in the network.
Number of modules (communities)	4	11	
Number of nodes in largest module	530 (module 0)	372 (module 4)	

Assortativity by the the Anatomical group

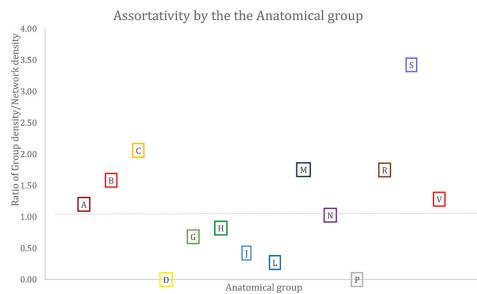


Fig. 6. Assortativity of network nodes in terms of similarity by the anatomical group. Squares above 1 represent a drug group with a higher density than the general density of the network (0.26). The S (Sensory organs) anatomical group had the highest assortativity. D (Dermatologicals) and P (Antiparasitic products) groups had no edges because these drug classes were excluded from the study.

Table 2

The top 10 clinically relevant severe DDIs in the co-medication network.

The severe DDI drug pair		No. of patients co-medicating
1	Codeine and paracetamol	Tramadol 855
2	Esomeprazole	Clopidogrel 823
3	Simvastatin	Carbamazepine 480
4	Metoprolol	Paroxetine 454
5	Metoprolol	Verapamil 380
6	Lansoprazole	Clopidogrel 308
7	Diclofenac	Ibuprofen 305
8	Diazepam	Oxazepam 300
9	Carbamazepine	Zopiclone 280
10	Omeprazole	Clopidogrel 277

Table 3

The top 10 combined drugs in the co-medication network.

Most combined drugs		No. of patients co-medicated
1	Acetylsalicylic acid	Simvastatin 82948
2	Acetylsalicylic acid	Metoprolol 52577
3	Acetylsalicylic acid	Atorvastatin 42753
4	Metoprolol	Simvastatin 36792
5	Acetylsalicylic acid	Amlodipine 32628
6	Acetylsalicylic acid	Zopiclone 29173
7	Amlodipine	Simvastatin 22554
8	Acetylsalicylic acid	Ramipril 19660
9	Simvastatin	Zopiclone 18845
10	Metformin	Acetylsalicylic acid 18507

predicting successful aging.⁴¹ These approaches are interesting and represent an alternative method to the other variable selection methods. Edge-level measures are the core of the networks and the principal for many network measures.

Modularity analysis exposes the network structure. This measure is believed to introduce special importance in the drug study. Bazzoni et al. found the DPN to be modular,¹⁹ which is consistent with what we found in our networks. Further investigation is needed to assess the underlying patterns in the modules we found in our co-medication network. Modules can be interpreted as clusters of patients with similar diagnoses using the same medications. In our initial analysis of modularity, we identified 4 modules, further work could be done to identify smaller groups by detecting the sub-clusters inside each module. Modules in the DDI network could be connected to pharmacological data to see the importance of pharmacokinetic interactions through systems such as the cytochrome P450 system. We have not explored this but there is a great

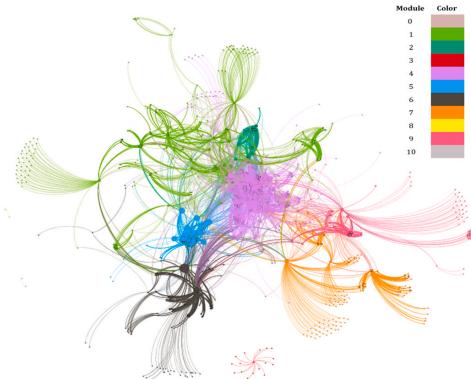


Fig. 7. The 11 modules that were detected in the severe DDIs network. Different colors indicate different modules. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

potential in using modularity analyses in order to understand networks.

Comparing different networks can reveal the change in patterns over time, place and different populations. Networks that describe the relation between drug-use and morbidities for a patient or a group of similar patients over time may identify the development of co-morbidities and drug use.

Bipartite networks provide a variety of possibilities to study many situations in which drugs are involved with other network actors such as physicians or diseases. Dasgupta & Chawla created a bipartite drug-disease network to study the interactions between drugs and co-morbidities.⁴² Hu et al. studied the prescribing of some opioids by creating a bipartite network of patients and prescribers and using the network to analyze the relationship between patients and prescribers and detect “doctor shopping” and suspicious network nodes.⁴³ A redrawn example from this study is shown in Fig. 8.

Our study has some limitations. As we used the DDD to outline the treatment episodes, we excluded the medications that have no defined DDD. This reduced the represented co-medication in our networks to the actual co-medication at the index date.

NA also has some important limitations. As a tool, it can be used to explore data, to find unusual structures, group nodes together and find unusual individual nodes. However, it can be hard to interpret results from NA and it is only suited for hypothesis generation. It also cannot explore many sets of relationships between variables at the same time as well as determining causal relationships. For such research questions, other hypothesis testing methodologies will be more needed. However, in research focused on exploration, NA can be a valuable tool.

Conclusion

The main purpose of this paper was to demystify the NA as a method. We have explained the terminology of network analyses and showed, with examples, how network analyses can be used for hypothesis generation. The online links to our networks visualize the data much better than a static picture can and we hope that we have provided enough information, and inspiration, to explore how you can use NA on your own data. We are confident that the future will see many new applications of NA and interesting results for researchers in social pharmacy and pharmacoepidemiology.

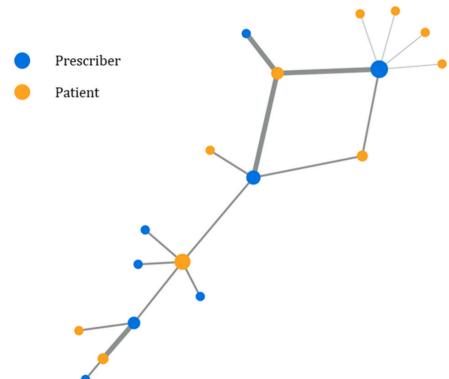


Fig. 8. An example of a bipartite network representing a sub-graph of two types of nodes (i.e. prescribers and patients) linked by the number of Fentanyl® patches prescriptions. The bigger nodes indicate more number of connections. The thicker edges indicate a higher number of prescriptions. (redrawn from “Network analysis and visualization of opioid prescribing data”⁴³).

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CRediT authorship contribution statement

Mohsen Askar: Conceptualization, Methodology, Software, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Raphael Nozal Cañas:** Software, Writing – review & editing. **Kristian Svendsen:** Conceptualization, Software, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no conflicts of interest related to this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sapharm.2021.06.021>.

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Appendix B: Preliminary Results

In this chapter, we explore the latest findings and ongoing research that form a crucial part of my PhD work. These results bear significant relevance to this thesis and enrich our understanding of the research domain, although still in progress and yet to be formally published. By including these preliminary findings, we aim to provide a comprehensive and up-to-date exploration of the topic. It is important to note that these findings are presented as drafts and are subject to further refinement and validation before publication.

B.1 Result I

Social network influences on obesity in a general youth population.

In recent years studies have evaluated the effect of peer pressure on obesity, via close friend networks in adults [10, 229, 230] and adolescents [231], or direct advertising of junk food [232] or healthy habits [233]. These studies have shown that people's health, including obesity, tends to become similar to those in their social network. We would like to check if these results also apply to our student population and how these evolve over time.

In these results (tables B.1, B.2 figures B.1, B.2), first, we showed the social dynamics with respect to BMI (table B.1). We show that this population behaves similarly to other student populations [234–236], and there is a bias in forming friendships with respect to BMI. "Overweight" and "Obese" students tend to form connections with each other, while at the same "Obese" students have lower connectivity and are more isolated in the network, and seem to have a negative bias towards "Healthy" students. On the other hand, "Healthy" form connections mostly among themselves, with a negative bias toward both "Overweight" and "Obese". Using the same simulation technique as in Paper A (section 4.1.9), we also show a bias toward obesity spread in all networks (table B.2), being stronger in the "Sports" network, and weaker in the "School" network.

Table B.1: Bias with respect to the total number of relationships between each BMI category. The top column shows the absolute and relative frequencies of the population ($n = 1034$). People with unknown BMI are excluded from the analysis ($n = 4$). Each combination of categories represents people who nominate a friend (rows) and people who are nominated (columns). Each cell is divided into three parts, the left-most is the total number of relationships in this combination, the center one is the expected number of relationships (only given if a bias was found), the right part contains an arrow indicating over (up ↑) or underrepresented (down ↓) using a two-sided binomial test with at least $p\text{-value} < 0.1$. The table χ^2 test is $< 10^{-10}$. In the bottom and to the left, we have the marginal absolute and relative frequencies for each combination.

	Underweight $n = 110, f = .106$	Healthy $n = 710, f = .684$	Overweight $n = 147, f = .142$	Obese $n = 67, f = .064$	Total	Freq
Underweight	47	285	48	24	404	10.8%
Healthy	282	1870 (1822)	345 (367) ↑	90 (122) ↓	2587	69.1%
Overweight	46	347	97 (74) ↑	34 (24) ↑	524	14.0%
Obese	22	135 (160) ↓	42 (32) ↑	29 (10) ↑	228	6.1%
Total	397	2637	532	177	3743	
Frequency	10.6%	70.5%	14.2%	4.7%		100%

Table B.2: Results of the spread of BMI across all networks simulations. The first column is the name of the network. Second is how many relationships are in that network. The third column is how many of those relationships share the same BMI category. The next 7 columns are the details of the simulation results, with the important one being the "Average" and "SD (Standard Deviation)", which shows how many same-to-same relationships in average we had in the 1000 simulations, using a network with the same topology but randomizing the BMI according to the BMI probability density data of the original network. The last column is the p-value, rounded to 3 decimals, which shows if there is a significant difference between the averaged same-to-same simulated relationship and the real same-to-same relationships.

Network	Real networks		Simulated 1000 networks							P-value
	Total Relationships	Equal Relationships	MIN	Q1	Median	Average	Q3	MAX	SD	
Overall	3767	2043	1761	1853	1893	1894.1	1934	2077	59.5	0.006
Physical	2823	1584	1233	1368	1402	1406.1	1445	1561	59.6	0.001
School	2979	1590	1337	1459	1490	1493.7	1536	1647	59.9	0.054
Sports	598	415	257	289	303	301.9	314	355	19.1	<0.0001
Home	1247	722	563	603	621	624.3	645	709	29.9	0.001
Other	1095	612	488	532	552	552.7	575	623	28.8	0.020

We checked for the general evolution of BMI over time (figure B.1). We observed that roughly half of the "Underweights" go into the "Healthy" group while almost none of the "Healthy" descent into the "Underweights". However, a similar trend is seen with a big group of "Healthy" going into "Overweight" without barely "Overweight" descend-

ing into “Healthy”. There is also another group going from “Overweight” to “Obese”; this group is larger than the group descending to “Healthy”. Both “Underweight” and “Healthy” groups decrease in size while both “Overweight” and “Obese” increase. Some from the “Obese” group descent into the “Overweight” group, but not enough to compensate for those new students entering the group. The average BMI (kg/m^2) in FF1 was 22.57 ± 4.23 , and in FF2 was 23.32 ± 4.25 . For men, in FF1 was 22.51 ± 4.22 and 23.55 ± 4.19 in FF2. For women was 22.62 ± 4.24 in FF1 and 23.12 ± 4.30 in FF2.

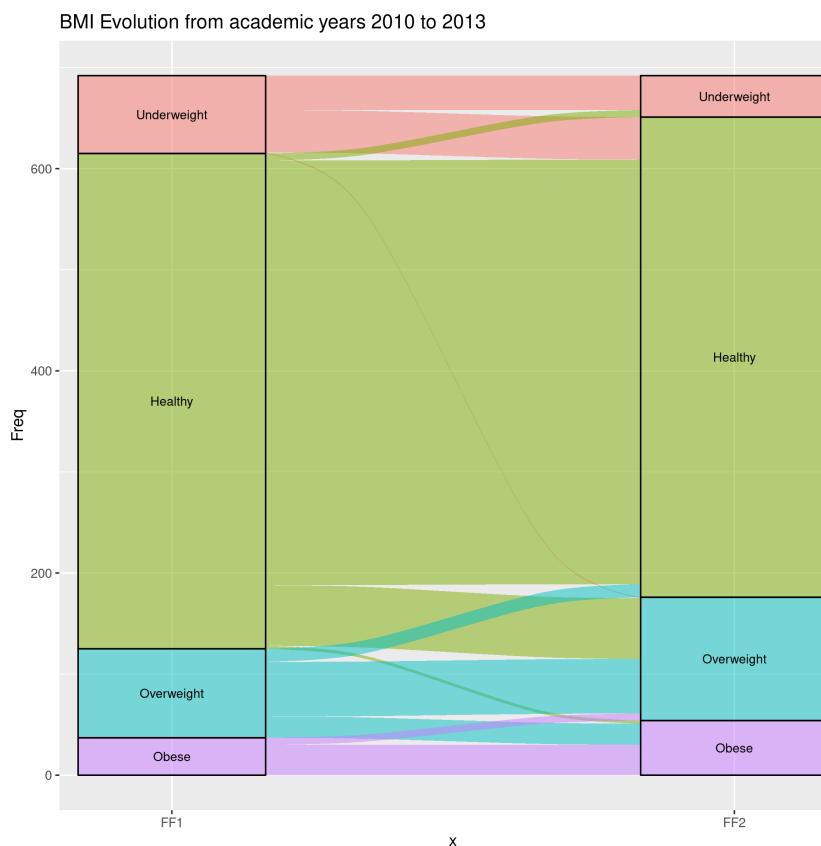


Figure B.1: An overview of the evolution of BMI from Fit Futures 1 (2010-2011) to Fit Futures 2 (2012-2013) for every student with valid BMI data in both studies ($n = 692$). On the left column, we have the FF1 BMI categories. In the right column, we have the FF2 categories two years later. The threads from left to right indicate the evolution of each person with respect to the BMI category.

We also tested if the number of high BMI friends is related to the BMI value in FF2 (figure B.2). On average, the “Healthy” and “Underweight” groups tend to go down in FF2, the greater the number of friends with $\text{BMI} > 25$ they had during FF1. We only see a sharp decrease in “Overweight” for the number of friends equal to 5, but they go into the “Obese” category instead which is a sharp increase in this group. Using logistic regression we estimated an 8.5% increase in the risk of high BMI with respect

to each additional "Overweight" or "Obese" friend. We also show that as the number of friends in FF1 with $BMI > 25$ increases, there is a higher probability of not landing in the "Healthy" group in FF2, and is also likely that the student will land in "Overweight" or "Obese" instead.

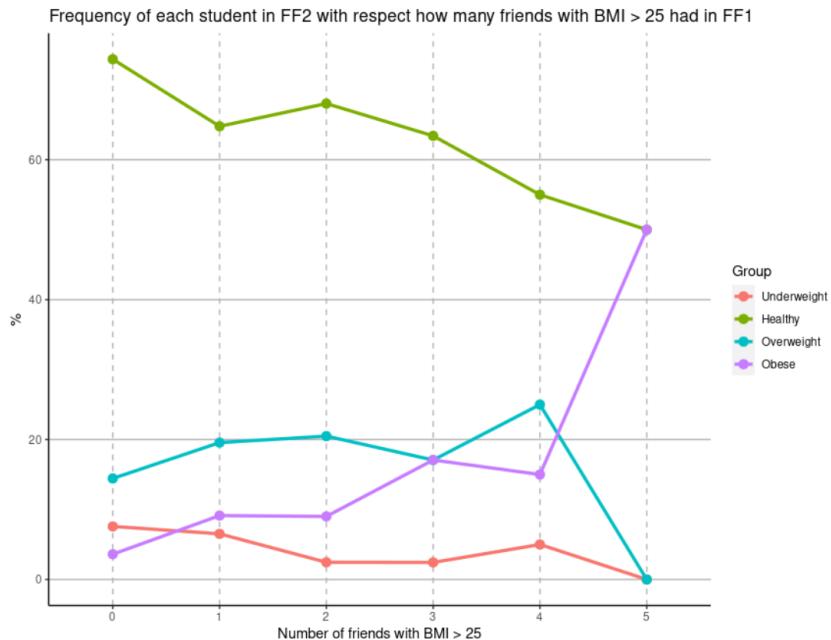


Figure B.2: The influence of friends from FF1 have with respect to FF2 BMI. The X-axis is the number of friends in FF1 with $BMI > 25 \text{ kg/m}^2$ The Y-axis is the relative number of students belonging to each BMI category in FF2.

Overall, these results seem to indicate that friendship is stagnated and students tend to keep within the same BMI group. And more importantly, an individual with "Healthy" friends has a better chance of being "Healthy" in the future, and an individual with "Overweight" or "Obese" friends has also a better chance of being "Overweight" or "Obese" in the future as well.

B.2 Result II

Social network influences on inflammatory response in a general youth population.

Chronic inflammation is a health concern with evidence suggesting that it contributes to the pathogenesis of numerous diseases, including cancer, cardiovascular disease, diabetes, and neurodegenerative disorders. Obesity has been shown to be correlated from childhood to adulthood [237], while also being responsible for a range of

adverse health conditions. Inflammation is shown to vary as a function of social isolation; in particular social behavior and the inflammatory process seem to be regulating one another [195, 238–243]. Obesity is also an underlying condition in both chronic inflammation and metabolic diseases [238, 244, 245]. In this explorative study, we investigate how the three concepts of inflammation in the form of a 92 proteomic assay, obesity in the form of anthropometric variables, and social interaction in the form of our network of friends, are related to one another. In particular, we look if there is a similarity of inflammation among social contacts. We found some results in the data that suggest that inflammatory markers are common among friends of the same sex and the same high school suggesting that social influence has an underlying link.

To evaluate if there is a correlation between each person and his/her friends' biomarker levels, we tried regression models (linear, quadratic, logarithmic, or exponential) using each person's friends' average biomarker level as the independent variable, and the person's biomarker levels as the dependent variable. Without any stratification by sex or by high school, we found no statistically relevant results for any biomarker. We found no correlation for sex stratification using all high schools. But biomarker levels are influenced by sex and social influence is driven by high school. If we stratify by these two variables; we found a total of 50 biomarkers for men and 46 for women that are significant with respect to some high schools (tables B.3 and B.4). This suggests that some biomarker levels are influenced by the student's social network, and in particular by high school, which has a relevant homophily coefficient (87.85% p-value <0.0001). Furthermore, high schools where blood samples were extracted later during the academic year (March / April 2011) show a higher amount of biomarkers correlation in contrast with other schools (October 2010 to March 2011). For High School 5, we found 13 markers for men, 11 for women; for High School 6, 23 for men, 17 for women; and for the rest of high schools combined 14 for men, 18 for women.

We wanted to check not only that biomarkers are similar among friends, but also different from non-friends. We defined biomarker distance as the ratio of the average square difference between each person's biomarker level and levels among students who are not his/her friends, and the average square difference between each person's biomarker level and levels among students who are his/her friends. We analyzed using same-sex friends, only for people with at least two friends of the same sex with valid biomarker levels. Values closer to 1 indicate no difference between each person's friends and non-friends biomarker level average. Values greater than 1 indicate that the distance to the friends' biomarkers is shorter (more similar) than to the non-friends biomarkers.

Values smaller than 1 indicate that non-friends are closer and more similar than friends. We arbitrarily defined distances ± 0.1 from 1 as relevant. We found for both men and women 14 proteins in each group with a ratio higher than 1.1, for men we found three proteins lower than 0.9, and for women, we found five proteins lower than 0.9 (tables B.5, B.6, B.7, B.8).

There is also a correlation between anthropometry and inflammation (table B.9 and table B.10); Result I and Result III suggest that social contact also influences the spread of obesity which is determined by anthropometrical variables. Not all the biomarkers presented in the anthropometric variables are necessarily expressed in each high school or vice versa. Inflammation driven by obesity only, or social influence only, would have similar results in both groups, so this would hint that we have a mix of the two factors. Furthermore, we see that high schools 5 and 6 have the greatest number of biomarkers being significant compared with the rest. This seems to indicate that biomarker levels gain similarity between friends over time. We also saw that the biomarkers that were negatively correlated with respect to friends' influence do not correlate with anthropometry and very little with high schools.

These results indicate, in the context of inflammation, that friendship either influence directly the immune system among a cluster of friends, or clusters of friends share some common habits which influence their immune system the same way.

Table B.3: Overview of all biomarkers with respect to each high school (n=8) for men. All biomarkers with either R² < 0.2 and p-value > 0.05, are hidden from the tables. P-values are expressed in GP Prism 5.04/d format.

Highschool	Protein	R2	P-value
H2	C-X-C motif chemokine 9	0.26	*
	Eotaxin	0.33	**
	Interleukin-10	0.55	****
	Interleukin-10 receptor subunit alpha	0.25	**
	Interleukin-13	0.66	****
	Interleukin-33	0.27	**
	Interleukin-6	0.28	*
	Interleukin-8	0.24	**
H3	Macrophage colony-stimulating factor 1	0.49	****
	Oncostatin-M	0.26	*
H4	Cystatin D	0.21	**
	STAM-binding protein	0.23	***
H5	Leukemia inhibitory factor receptor	0.27	***
	Adenosine Deaminase	0.44	****
	Beta-nerve growth factor	0.22	**
	C-C motif chemokine 28	0.28	**
	C-X-C motif chemokine 11	0.21	*
	CD40L receptor	0.29	**
	CUB domain-containing protein 1	0.23	*
	Fractalkine	0.48	***
	Interleukin-10	0.21	**
	Interleukin-10 receptor subunit alpha	0.34	**
H6	Interleukin-17C	0.24	**
	Macrophage colony-stimulating factor 1	0.24	*
	Monocyte chemoattractant protein 3	0.21	**
	Tumor necrosis factor receptor superfamily member 9	0.4	***
	Artemin	0.32	*
	Beta-nerve growth factor	0.27	*
	C-C motif chemokine 20	0.57	**
	C-C motif chemokine 25	0.45	**
	C-C motif chemokine 28	0.62	***
	C-X-C motif chemokine 5	0.32	*
	C-X-C motif chemokine 6	0.4	*
	Caspase-8	0.49	**
	CD40L receptor	0.72	***
	CUB domain-containing protein 1	0.63	***
H7	Delta and Notch-like epidermal growth factor-related receptor	0.56	**
	Fibroblast growth factor 23	0.49	**
	Fractalkine	0.41	*
	Interferon gamma	0.4	*
	Interleukin-33	0.28	*
	Interleukin-8	0.57	**
	Leukemia inhibitory factor receptor	0.49	**
	Neurotrophin-3	0.51	**
	Oncostatin-M	0.28	*
	Osteoprotegerin	0.53	**
H8	Programmed cell death 1 ligand 1	0.47	**
	TNF-related apoptosis-inducing ligand	0.48	**
	Urokinase-type plasminogen activator	0.65	***

Table B.4: Overview of all biomarkers with respect to each high school (n=8) for women. All biomarkers with either R² < 0.2 and p-value > 0.05, are hidden from the tables. P-values are expressed in GP Prism 5.04/d format.

Highschool	Protein	R ²	P-value
H1	Glial cell line-derived neurotrophic factor	0.26	****
	Interferon gamma	0.24	***
H2	Tumor necrosis factor	0.4	****
H4	Fibroblast growth factor 19	0.23	**
	Interleukin-10 receptor subunit beta	0.25	*
	Interleukin-33	0.29	**
	Matrix metalloproteinase-10	0.24	**
	Neurturin	0.31	***
	Programmed cell death 1 ligand 1	0.32	**
	STAM-binding protein	0.24	**
	Sulfotransferase 1A1	0.22	*
H5	Urokinase-type plasminogen activator	0.28	**
	C-C motif chemokine 28	0.27	**
	C-X-C motif chemokine 5	0.31	**
	C-X-C motif chemokine 9	0.21	*
	Interleukin-10 receptor subunit beta	0.27	***
	Interleukin-6	0.32	***
	Interleukin-7	0.22	**
	Latency-associated peptide transforming growth factor beta-1	0.26	***
H6	Matrix metalloproteinase-10	0.22	**
	TNF-related activation-induced cytokine	0.24	**
	Tumor necrosis factor	0.36	****
	Vascular endothelial growth factor A	0.24	**
	Brain-derived neurotrophic factor	0.76	**
	C-C motif chemokine 23	0.95	***
	Delta and Notch-like epidermal growth factor-related receptor	0.85	***
	Fibroblast growth factor 21	0.66	**
H8	Fms-related tyrosine kinase 3 ligand	0.76	*
	Interleukin-10 receptor subunit alpha	0.69	**
	Interleukin-17A	0.64	*
	Interleukin-2 receptor subunit beta	0.75	*
	Interleukin-20 receptor subunit alpha	0.73	**
	Interleukin-33	0.64	**
	Interleukin-6	0.9	***
	Leukemia inhibitory factor receptor	0.89	***
	Monocyte chemoattractant protein 3	0.78	**
	Neurturin	0.45	*
	Osteoprotegerin	0.59	*
	Stem cell factor	0.67	**
	T cell surface glycoprotein CD6 isoform	0.45	*
	C-C motif chemokine 4	0.27	***
	Caspase-8	0.47	****
	Interleukin-17C	0.21	**
	Interleukin-24	0.36	****
	Osteoprotegerin	0.21	**
	Tumor necrosis factor receptor superfamily member 9	0.29	***

Table B.5: Ratio of average square distances between each person's biomarker level and friend's biomarker levels, and average square distance between each person's biomarker levels and non-friends biomarker levels. Values greater than 1 suggest that clusters of friends have similar biomarkers levels in comparison with the rest of the non-friend population. Relevant values are highlighted in bold, with green for >1.1 and red for <0.9. Values are rounded to two decimals but highlighted according to the original values. (Table 1 of 4)

Protein	Men	Women
Adenosine Deaminase	1.12	1.03
Artemin	0.98	1.04
Axin-1	1.06	1.02
Brain-derived neurotrophic factor	1.06	1.14
Beta-nerve growth factor	1.29	0.91
Caspase-8	1.01	1.04
Eotaxin	0.94	1.04
C-C motif chemokine 19	1	0.96
C-C motif chemokine 20	1.09	0.97
C-C motif chemokine 23	1.06	1.1
C-C motif chemokine 25	1.04	1.02
C-C motif chemokine 28	0.76	0.84
C-C motif chemokine 3	1	0.96
C-C motif chemokine 4	0.98	1.02
Natural killer cell receptor 2B4	1.02	1
CD40L receptor	1.03	1.04
T-cell surface glycoprotein CD5	1.09	1.07
T cell surface glycoprotein CD6 isoform	1.04	0.97
CUB domain-containing protein 1	1.04	1.14
Macrophage colony-stimulating factor 1	1.01	1.13
Cystatin D	1.04	0.97
Fractalkine	1.12	1.03
C-X-C motif chemokine 1	1.07	1.08
C-X-C motif chemokine 10	1.05	0.97

Table B.6: Ratio of average square distances (Table 2 of 4)

Protein	Men	Women
C-X-C motif chemokine 11	1.05	1.02
C-X-C motif chemokine 5	1.01	1.09
C-X-C motif chemokine 6	0.95	1
C-X-C motif chemokine 9	1.11	1
Delta and Notch-like epidermal growth factor-related receptor	1.14	1.09
Eukaryotic translation initiation factor 4E-binding protein 1	1.21	1.03
Protein S100-A12	1.03	0.99
Fibroblast growth factor 19	1.08	1.06
Fibroblast growth factor 21	1.07	1.12
Fibroblast growth factor 23	1.08	1.06
Fibroblast growth factor 5	1.03	0.9
Fms-related tyrosine kinase 3 ligand	1.11	0.99
Glial cell line-derived neurotrophic factor	1.08	1.05
Hepatocyte growth factor	1.04	1
Interferon gamma	1.04	0.79
Interleukin-10	0.99	1.16
Interleukin-10 receptor subunit alpha	1.03	0.96
Interleukin-10 receptor subunit beta	1.1	1.06
Interleukin-12 subunit beta	1.08	1
Interleukin-13	1.04	1.11
Interleukin-15 receptor subunit alpha	1.02	1
Interleukin-17A	0.95	1
Interleukin-17C	1.06	1.04
Interleukin-18	0.97	1.05

Table B.7: Ratio of average square distances (Table 3 of 4)

Protein	Men	Women
Interleukin-18 receptor 1	0.94	1.08
Interleukin-1 alpha	1.09	1.12
Interleukin-2	1.09	0.97
Interleukin-20	1.22	0.98
Interleukin-20 receptor subunit alpha	1.01	0.98
Interleukin-22 receptor subunit alpha-1	1	0.92
Interleukin-24	0.98	1.03
Interleukin-2 receptor subunit beta	1.05	0.93
Interleukin-33	1.03	0.99
Interleukin-4	0.98	1.09
Interleukin-5	0.87	1.04
Interleukin-6	0.98	1.3
Interleukin-7	1.03	1
Interleukin-8	1.05	1.01
Leukemia inhibitory factor	0.92	0.85
Leukemia inhibitory factor receptor	1.08	0.96
Monocyte chemotactic protein 1	1.05	1.18
Monocyte chemotactic protein 2	0.92	1.06
Monocyte chemotactic protein 3	1.01	0.92
Monocyte chemotactic protein 4	1	1.12
Matrix metalloproteinase-1	1.05	0.97
Matrix metalloproteinase-10	1.11	1.1
Neurturin	0.91	1.06
Neurotrophin-3	0.98	1.02

Table B.8: Ratio of average square distances (Table 4 of 4)

Protein		Men	Women
Osteoprotegerin		1.07	0.98
Oncostatin-M		1.09	1.03
Programmed cell death 1 ligand 1		0.93	0.96
Stem cell factor		1.05	1.08
SIR2-like protein 2		1.04	1.02
Signaling lymphocytic activation molecule		1.02	0.88
Sulfotransferase 1A1		1.01	1.07
STAM-binding protein		1.1	0.99
Transforming growth factor alpha		1.09	1.02
Latency-associated peptide transforming growth factor beta-1		1.08	0.99
Tumor necrosis factor		0.87	0.69
TNF-beta		1.04	1.02
Tumor necrosis factor receptor superfamily member 9		1.24	1.08
Tumor necrosis factor ligand superfamily member 14		1.08	1.01
TNF-related apoptosis-inducing ligand		1.17	1.01
TNF-related activation-induced cytokine		1.1	1.11
Thymic stromal lymphopoietin		1.01	0.98
Tumor necrosis factor		1.02	1.02
Urokinase-type plasminogen activator		1.24	1.08
Vascular endothelial growth factor A		1	1.16

Table B.9: Anthropometric variables with respect to biomarkers levels in men. Each cell is a p-value in GP Prism 5.04/d format. Biomarkers rows with no statistically significant p-values are hidden. All p-values are corrected for Bonferroni.

Protein	Waist	Hip	Height	Weight	BMI	HR	SYSBP	DIABP
C-C motif chemokine 3	***	**	ns	**	**	ns	ns	ns
C-C motif chemokine 4	**	ns	ns	ns	ns	ns	ns	ns
CUB domain-containing protein 1	****	****	ns	****	****	ns	ns	ns
Macrophage colony-stimulating factor 1	**	****	ns	***	***	ns	ns	ns
Delta and Notch-like epidermal growth factor-related receptor	ns	ns	ns	*	ns	ns	ns	ns
Fibroblast growth factor 19	ns	ns	ns	ns	*	ns	ns	ns
Fibroblast growth factor 21	*	ns	ns	ns	ns	ns	ns	ns
Glial cell line-derived neurotrophic factor	**	ns	ns	*	**	ns	ns	ns
Hepatocyte growth factor	****	***	ns	**	****	ns	ns	ns
Interleukin-18	***	***	ns	***	***	ns	ns	ns
Interleukin-18 receptor 1	****	****	ns	****	****	ns	ns	ns
Interleukin-6	****	***	ns	***	****	ns	ns	ns
Monocyte chemoattractant protein 3	****	****	ns	****	****	ns	ns	ns
Stem cell factor	****	****	ns	****	****	ns	ns	ns
Tumor necrosis factor receptor superfamily member 9	***	ns	ns	*	**	ns	ns	ns

Table B.10: Anthropometric variables with respect to biomarkers levels in women. Each cell is a p-value in GP Prism 5.04/d format. Biomarkers rows with no statistically significant p-values are hidden. All p-values are corrected for Bonferroni.

Protein	Waist	Hip	Height	Weight	BMI	HR	SYSBP	DIABP
Caspase-8	*	***	ns	***	**	ns	ns	ns
C-C motif chemokine 3	*	ns	ns	ns	ns	ns	ns	ns
CUB domain-containing protein 1	****	****	ns	****	****	ns	ns	ns
Macrophage colony-stimulating factor 1	****	***	ns	**	**	ns	ns	ns
Delta and Notch-like epidermal growth factor-related receptor	ns	ns	ns	*	*	ns	ns	ns
Fibroblast growth factor 21	*	ns	ns	ns	*	ns	ns	ns
Hepatocyte growth factor	****	***	ns	**	***	ns	ns	ns
Interleukin-10 receptor subunit beta	****	*	ns	**	**	ns	ns	ns
Interleukin-18	**	*	ns	ns	**	ns	ns	ns
Interleukin-18 receptor 1	****	***	ns	***	****	ns	ns	ns
Interleukin-6	****	****	ns	****	****	ns	ns	ns
Interleukin-7	**	**	ns	**	*	ns	ns	ns
Monocyte chemotactic protein 3	****	****	ns	****	****	ns	ns	ns
Monocyte chemotactic protein 4	*	ns	ns	ns	ns	ns	ns	ns
Latency-associated peptide transforming growth factor beta-1	*	*	ns	ns	ns	ns	ns	ns
TNF-related apoptosis-inducing ligand	**	*	ns	ns	*	ns	ns	ns
TNF-related activation-induced cytokine	*	**	ns	*	ns	ns	ns	ns
Vascular endothelial growth factor A	**	*	ns	*	****	ns	ns	ns

B.3 Result III

Measuring social influence with random forest regression and artificial neural networks

There are plenty of studies and machine learning models that predict obesity given a multivariate dataset, some using up to 190 multidomain variables [246]. But to our knowledge, no machine learning method has been used to predict changes in BMI using social networks and compare how well the model evaluate those variables' score to classical lifestyle factors.

We want to determine which variables are more important to predict BMI in FF2. We measured the influence of host factors, and the influence of the total number of friends grouped by BMI category, using RF (easier explainability) and ANNs (higher accuracy). We measure variable influence using SHAP for both models and MDI for RF.

We split our subjects into six different datasets, organized by whether or not the student's BMI increased or decreased, and which was the original BMI in FF1.

- **(A) “Getting worse or staying bad”.** Cases for students who are Healthy in FF1 and end up Overweight or Obese in FF2. Or students who are Overweight in FF1 and end up Overweight or Obese in FF2. Or students who are Obese in FF1 and stayed Obese in FF2.
- **(B) “Getting better or staying good”.** Cases for students who are Healthy, Overweight, or Obese BMI in FF1 and end up Healthy in FF2. Or Obese BMI in FF2 and end up Overweight in FF2.
- **(C) “Stay Healthy”.** Cases for students who have a Healthy BMI in both FF1 and FF2.
- **(D) “Bad cases get strictly better”.** Cases for students who have FF1 BMI > 25, and their FF2 BMI < FF1 BMI.
- **(E) “Healthy to worse”.** Cases for students with a Healthy BMI in FF1, who have a FF2 BMI > 25.
- **(F) “Overweight or worse get strictly worse”.** Cases for students with FF1 BMI > 25, who have a FF1 BMI < FF2 BMI

We run both models against every dataset (table B.11). We also measured all the mean SHAP absolute values with respect to every dataset, every model, and every variable (figure B.3). Initial BMI in FF1 is always ranked as a very important variable in every model. In general, individual social influence variables are also highly ranked among sex and sport frequency. Dataset E seems to stand up with respect to the rest due to variable importance being quite different and more balanced across each variable. RF tends to lower the importance of any variable that is not BMI, while ANN tends to give more importance to the rest of the variables. Furthermore, we also tested all variables MDI with respect to all RF models (figure B.4).

Table B.11: Summary of all models and datasets used. From left to right, the ID of each dataset is represented by a letter, the short name of the dataset, the total samples in the dataset, Mean Absolute Error (MAE) for each model (RF or ANN) performing in this dataset, mean BMI in FF1 and mean BMI in FF2 in this dataset.

ID	Name	Samples	MAE		Mean BMI	
			RF	ANN	FF1	FF2
A	Healthy or worse to Overweight or worse	168	1.71	1.81	26.88	29.07
B	Healthy or worse to Healthy or better	440	0.99	1.00	21.43	21.98
C	Healthy to Healthy	420	1.05	1.07	21.12	21.81
D	Overweight or worse to lower BMI	44	0.96	1.39	28.69	26.79
E	Healthy to Overweight or worse BMI	63	0.90	1.60	23.32	26.52
F	Overweight or worse to higher BMI	80	1.86	1.95	28.99	31.46

On average, the models presented a Mean Absolute Error (MAE) of 1.35, and evaluated either "Total Healthy Friends" or "Total Overweight Friends" as either the most important variable or among the top 3 more important, for all models and datasets, after the variable BMI in FF1.

It is possible to evaluate specific individuals to check what makes them gain or lose BMI in FF2 with respect to FF1. Here we present two examples using RF in dataset A (figures B.5 and B.6). Individual cases should not be extrapolated as variable weights for the whole dataset.

Partial dependencies plots indicate how changing a particular variable changes the output of the model. All plots produced in this section are done using the RF models.

All datasets except C (Healthy to Healthy) show a decrease in BMI with respect to the total number of healthy friends (figure B.7). Datasets B (Overweight or Obese to

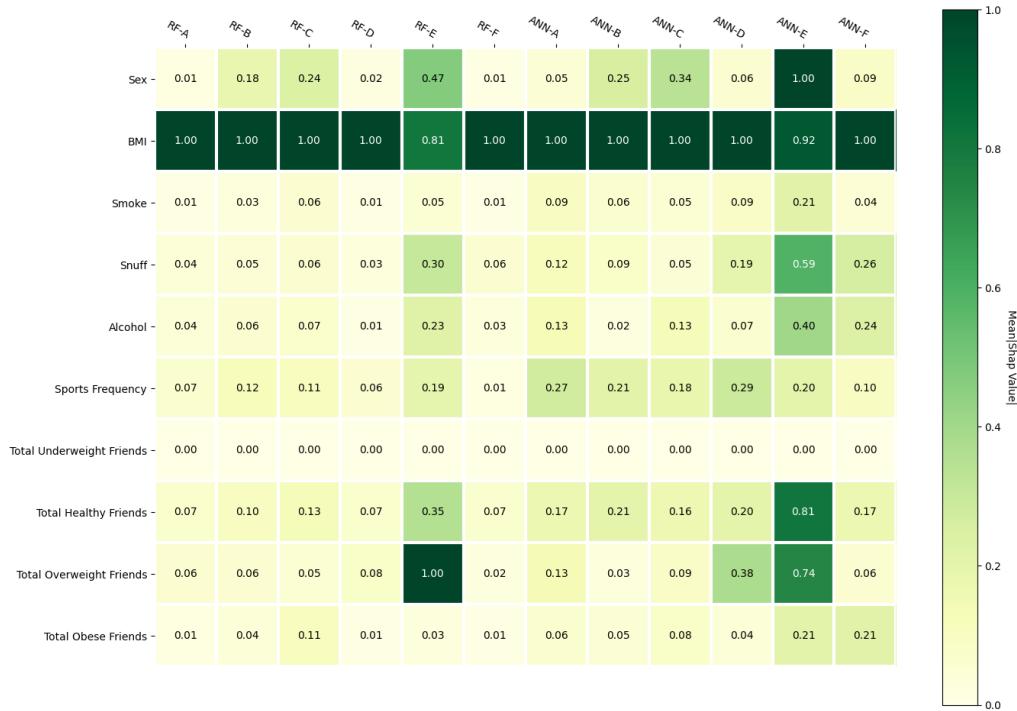


Figure B.3: Heatmap with the normalized mean $|SHAP\ values|$ for the model with respect to each dataset (top names) against each variable (left names). Values closer to 1 indicate strong importance in the model.

better) and C also show a slight increase in BMI with sports, this might be due to an increase in muscle mass and reduced total percentage of fat due to exercise. Increasing the BMI is not necessarily bad if the increase is due to a higher weight due to increased muscle mass. So, in the C dataset, this increase seems to be justified due to staying healthy. In the B dataset, it would indicate that sports also help by decreasing total body fat.

All datasets except for D (Overweight or worse got better BMI) showed an increase in BMI with respect to the total number of overweight friends (figure B.8).

The dependency plots show on average a very slight increase ($+0.12$) in the final BMI. The weight of this variable is also low in the RF models. We show in the friendship bias section that obese individuals have low popularity and are not well connected with the healthy group. For all combined 692 valid samples, the average of total overweight friends is 0.28 ± 0.56 . It would appear that increasing connectivity with obese individuals did not have a meaningful effect. However, since the connectivity is low, we can't extrapolate on how the effect would be in a better-connected population.

The E dataset (Healthy BMI that ends up in Overweight or worse) seems to have a completely different weight of SHAP values according to both RF and ANN (figure B.3), and to MDI in RF (figure B.4). Is also the group with the bigger BMI increase ($+3.2 \pm 1.6$). The variable Total Overweight friends get a very high impact on the model despite people not having that many overweight friends. In general, Total Healthy friends decrease the BMI but it shows a spike in BMI for specifically "3" healthy friends (figure B.7). It shows an increase with smoke but a decrease with snuff and alcohol frequency (figure B.9). Females have slightly more risk than males. We tried limiting the dataset from Healthy to Overweight only in case the Healthy to Obese jump was too much of an outlier, but it had barely any effect on the outputs. Analyzing all individuals one by one using the waterfall plots did not show any pattern. Dataset C shows a spike in BMI for "2" total numbers of healthy friends (figure B.7), but the model is more predictable. E is just a subset of the A dataset which does not show any strange particularities either.

Similarly to Result I, here we evaluate the influence of friendship on obesity and it appears that there's also an influence depending on the number of "Healthy", "Overweight", or "Obese" friends. And our machine learning models give a similar explanation compared with previous results.

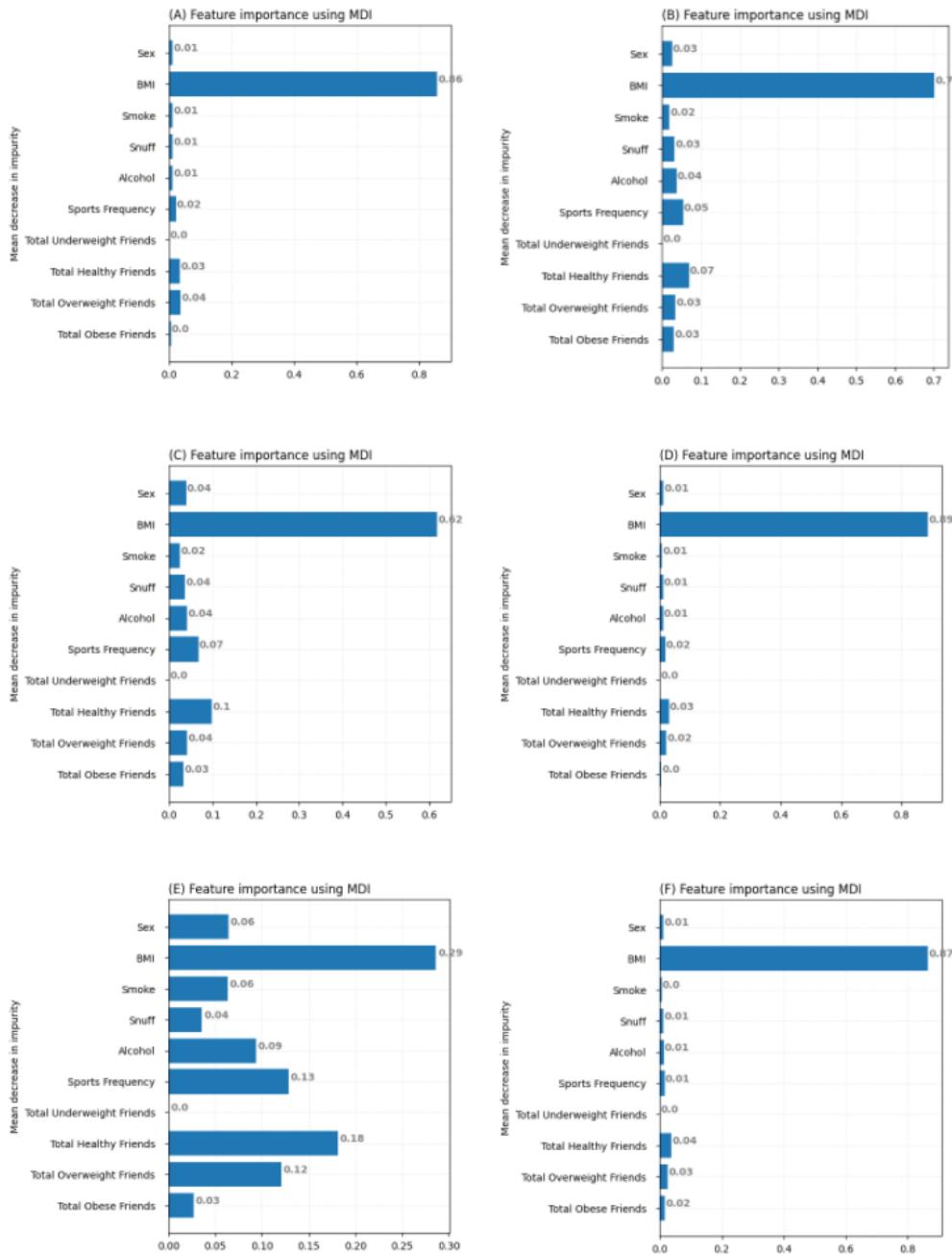


Figure B.4: Barplots using MDI in RF for each of the datasets. The x-axis represents the MDI value, the greater the value the greater the importance. The y-axis represents each of the studied variables.

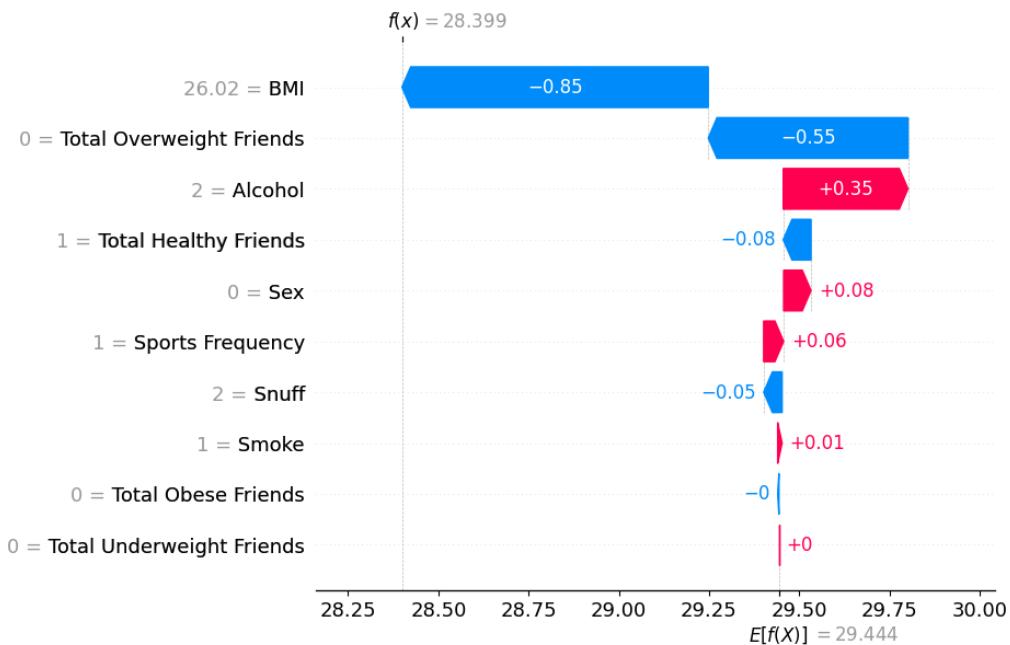


Figure B.5: Waterfall plot with an individual case in the (A) dataset. The first row is the initial BMI in FF1, which was 26.09 (overweight) but is relatively close to 25 and this person is almost classified as healthy. This contributed the most (-0.85) to the final BMI in FF2 displayed on the figure's top “ $f(x) = 28.399$ ”, which increases below average in comparison with the rest of the samples in this dataset; with the average being 29.444 displayed on the bottom of the figure as “ $E[f(X)] = 29.2444$ ”. After that, we see that having 0 overweight friends also contributed (-0.55) in favor of lowering the final BMI. The alcohol consumption of 2, equivalent to “Twice or more per month”, contributed in the opposite direction, increasing the final BMI to +0.35. One healthy friend contributed a little bit to decrease the final BMI. Being a man (sex = 0) contributed a little bit to worse BMI. And so on for the rest of the variables until the change becomes inconsequential.

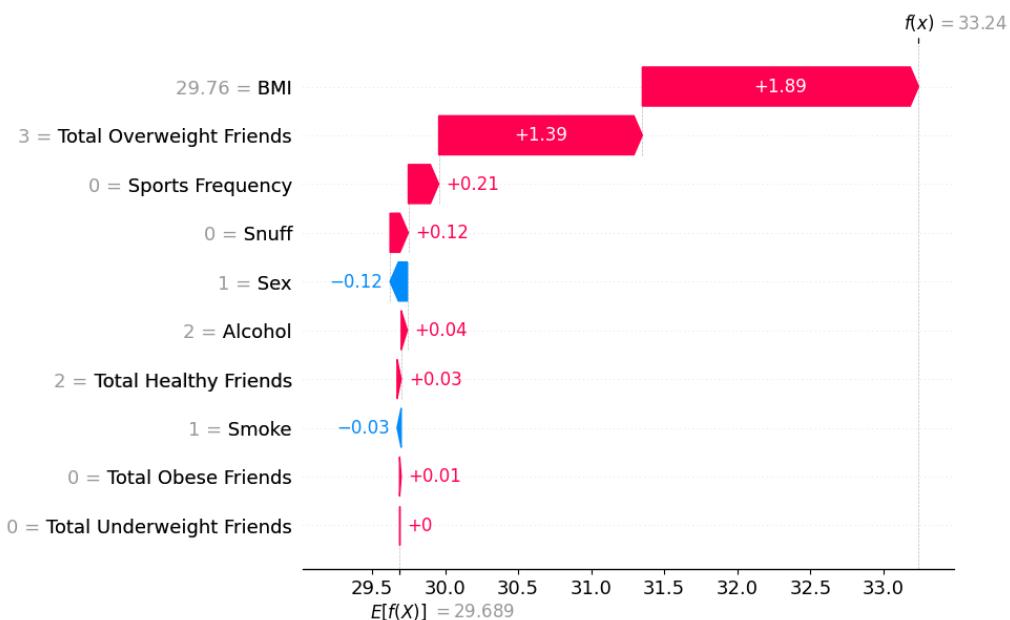


Figure B.6: Waterfall plot with an individual case in the (A) dataset. The initial BMI in FF1 was 29.68, very close to the obese category, which contributed the most to increasing the final FF2 BMI to 33.24, displayed in “ $f(x) = 33.24$ ” at the top of the figure, by quite a lot (+1.89), in comparison with the FF2 average displayed at the bottom of the figure as “ $E[f(x)] = 29.689$ ”. Having 3 overweight friends also contributed to a similar increase of +1.39. Not practicing any sport also contributed to a moderate increase in BMI (+0.21). The rest of the variables' effects' sizes are quite small in comparison to the effects of the first three.

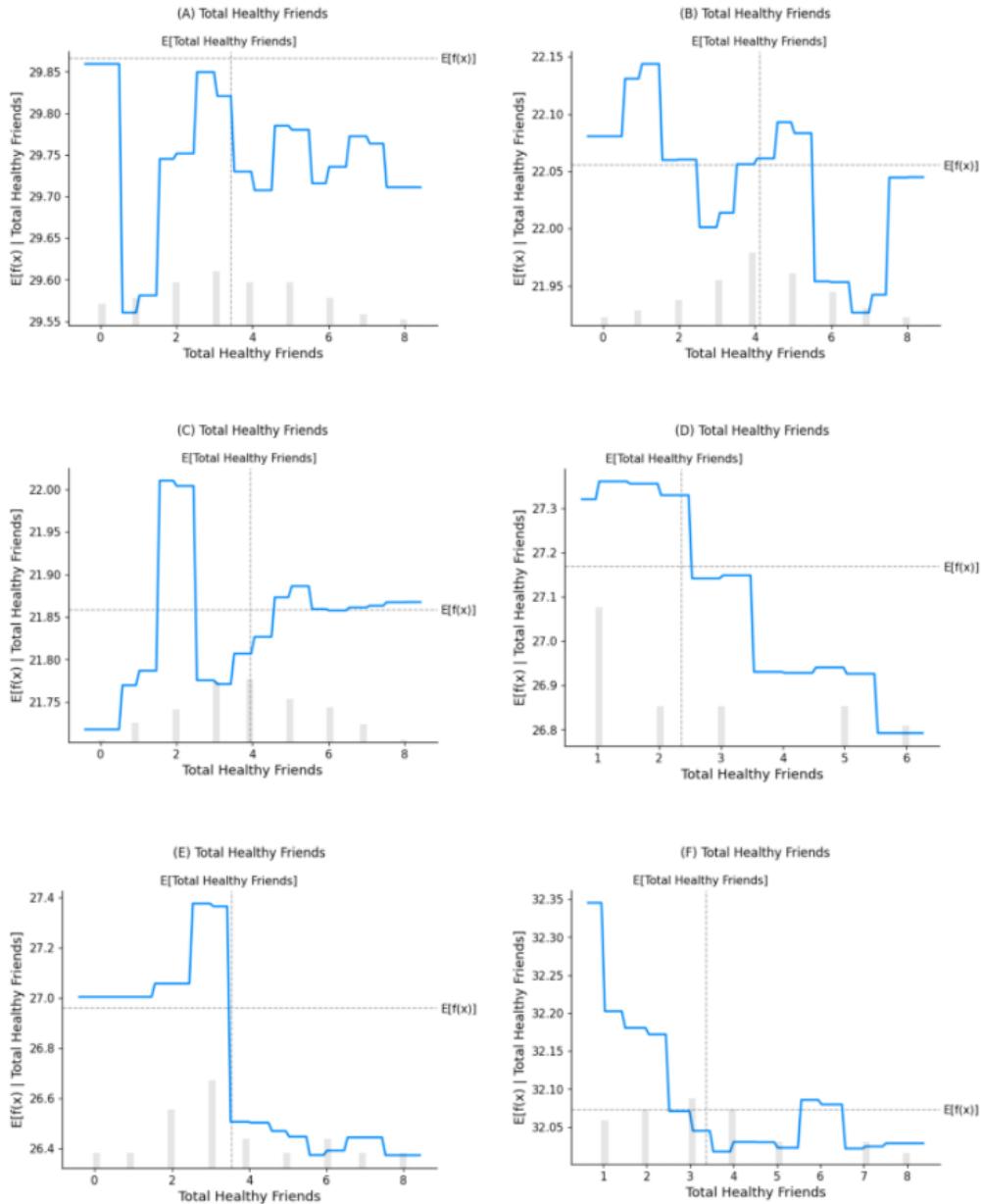


Figure B.7: Partial dependencies plots for datasets A to F in regard to total healthy friends for the RF models. On the X-axis, the total number of healthy friends, with a light grey histogram in the background. On the Y-axis, this variable is expected to modify the model output (BMI) as the variable changes.

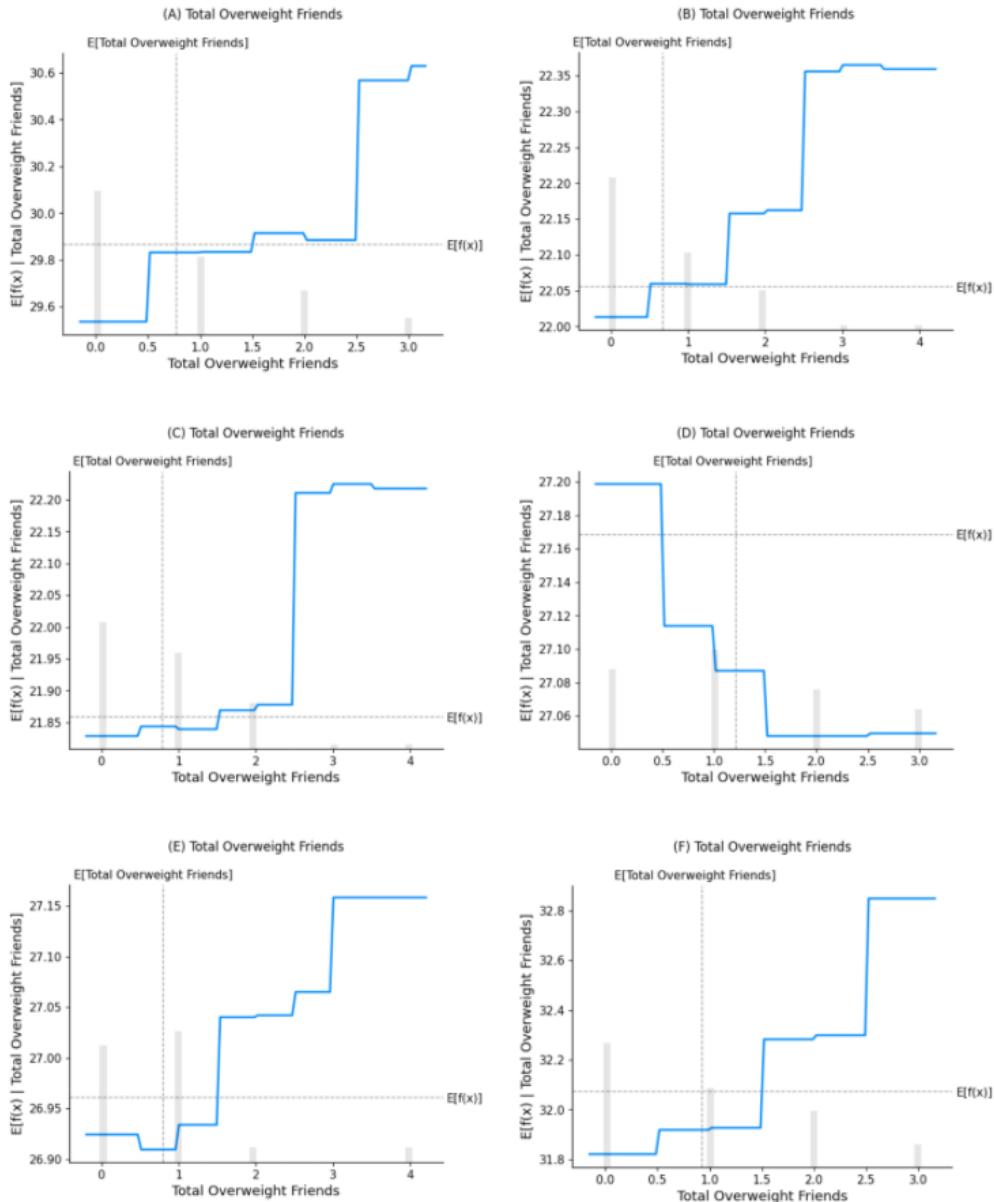


Figure B.8: Partial dependencies plots for datasets A to F in regard to total overweight friends for the RF models. On the X-axis, the total number of healthy friends, with a light grey histogram in the background. On the Y-axis, how this variable is expected to modify the model output (BMI) as the variable changes.

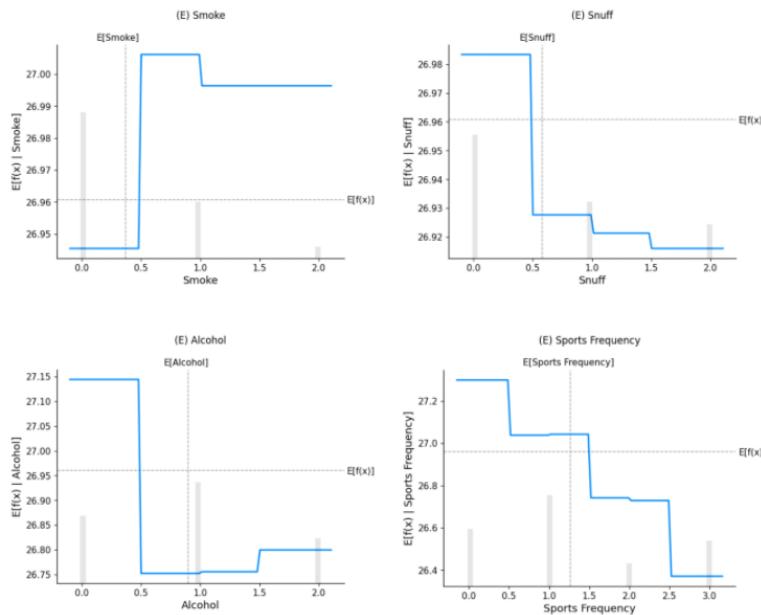


Figure B.9: Partial dependencies plots for datasets E regarding recreational drugs and sport frequency for the RF models. On the X-axis, the total number of healthy friends, with a light grey histogram in the background. On the Y-axis, how this variable is expected to modify the model output (BMI) as the variable changes.

B.4 Result IV

Frequency consumption of medication and social network influence in a general youth population.

In previous studies there has been a concerning trend in self-medication and in particular the overuse of painkillers for non-therapeutic purposes; mostly as a recreational drug within Norway [118, 247, 248] which coincide with worldwide trends and usage [114–117]. With this study, we aim for two objectives. First, to update the data on self-reporting medication with the FF1's 2010 data, and if possible, include up to Fit Futures 3 data done throughout the year 2022. And second to investigate if there's a social influence component as to whether students tend to self-medicate.

We analyzed the frequency of self-reported consumption of medicines and diseases in our population (figure B.10). We can observe that there are plenty of dermatological diseases, however, the usage of dermatological medicines is quite low. In contrast, the amount of pain-related diseases is low, but the consumption of painkillers, or anti-inflammatory medicaments is extremely high in comparison.

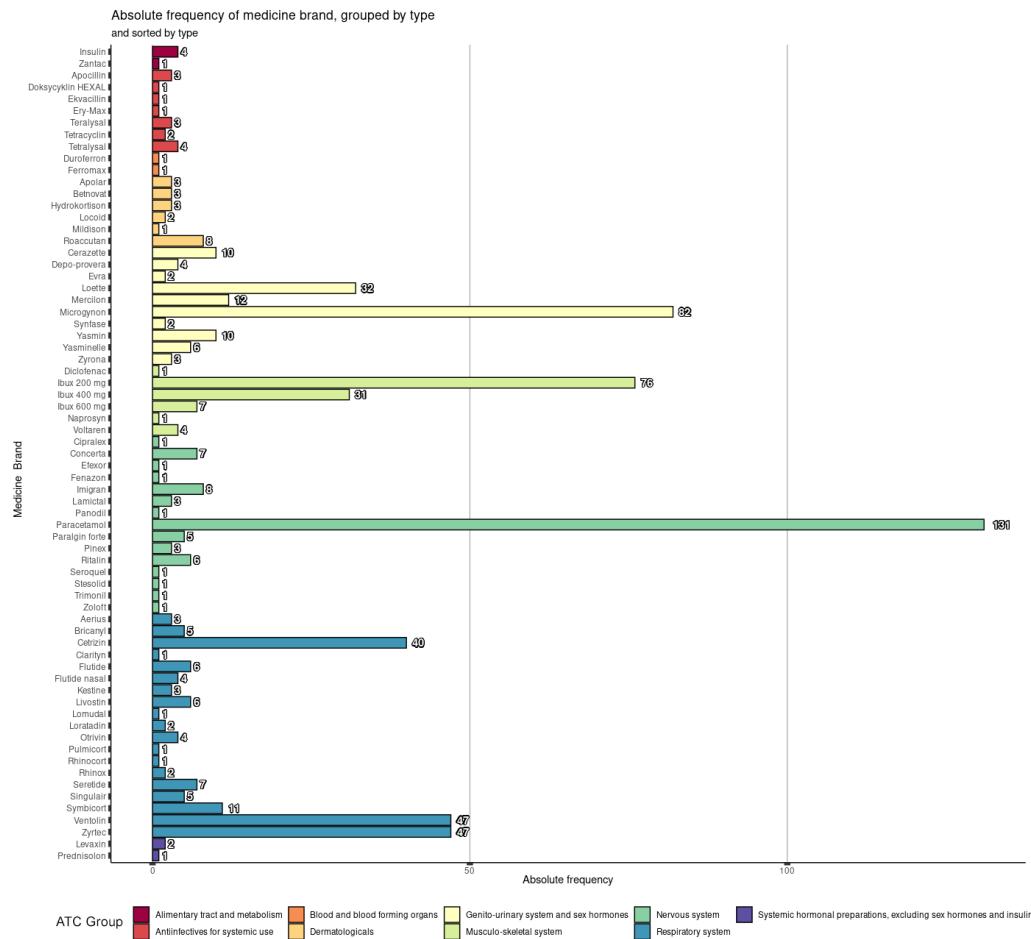


Figure B.10: Absolute frequency of medicine consumption sorted by ATC group. Hormonal contraceptives, anti-inflammatories, painkillers, antiasthmatic, and antihistaminics dominate the frequency of use.

Females seem to have a higher consumption of medicines in general (figure B.12), and also higher disease prevalence (figure B.11). However, the disease types and medicine types don't match; meaning that self-medication is higher among the female population.

Table B.12: Summary of the χ^2 significance for relevant medicine groups divided by bias type (high school and sex). From left to right, bias type, type of medicine, numerical significance rounded to 4 decimals, and p-value in GP Prism 5.04/d format. Hormonal contraceptives seem to be biased concerning high school. Painkillers also seem to be biased by high school and sex. Anti-inflammatory shows a bias by sex only

Bias type	Medicine	Significance	
Highschool	Hormonal contraceptives (women only)	0.0002	***
	Anti-inflammatory	0.2075	ns
	Antihistamine	0.1766	ns
	Painkiller	0.0006	***
Sex	Anti-inflammatory	0	****
	Antihistamine	0.264	ns
	Painkiller	0.0011	**

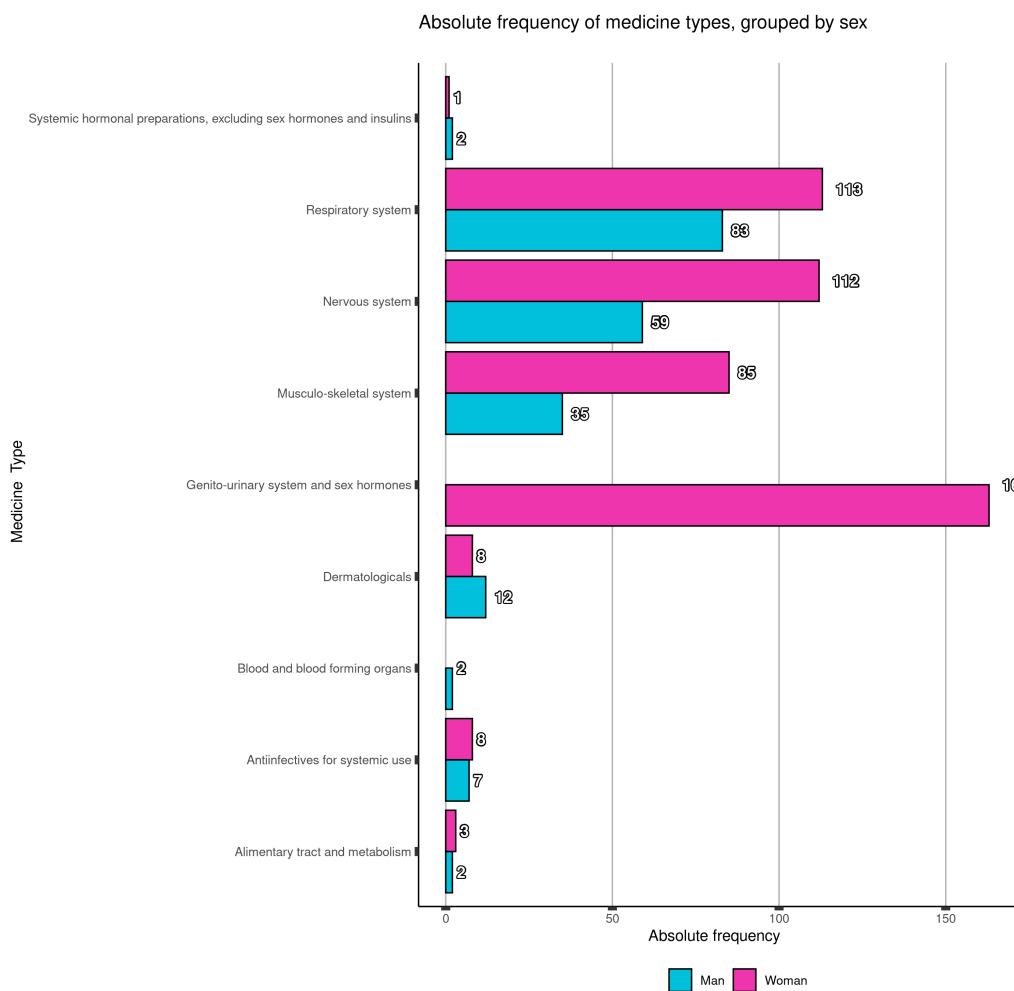


Figure B.11: Absolute frequency of medicine consumption group by ATC group and divided by sex, which seems to indicate a higher consumption among females

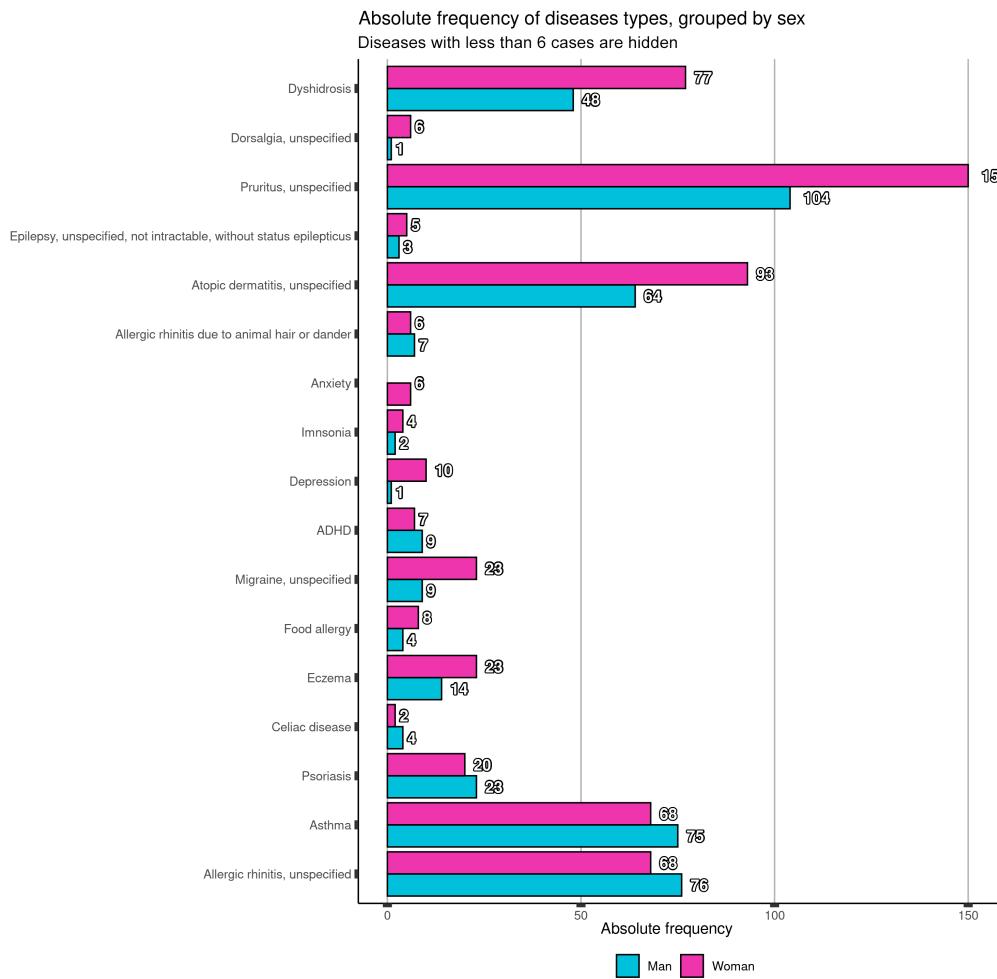


Figure B.12: Absolute frequency of self-reported diseases divided by sex. To avoid visual cluttering, diseases with 5 or fewer instances are not included in this figure. Females also lead in dermatological and psychological conditions, plus migraines. Males seem to have a short lead in respiratory conditions.

We analyzed if there was any bias concerning sex and high school using over-the-counter medicines and also concerning hormonal contraceptives in women. Our results (table B.12) indicate that women sharing the same high school is biased towards hormonal contraceptive usage. Our simulations also show that women who are friends are biased to share the same hormonal contraceptive brand. One of the possible reasons is due to direct recommendations among them and later on asking their family doctor for the same brand. Another one is that women going to the same school tend to live close by and thus share the same family doctor who tends to prescribe the same medication.

The results coincide with teenagers' trend of misusing over-the-counter medication.