أخلاقيات البحث العلمى

ETHICS IN MEDICAL RESEARCH

What is research:

- Performing a methodical study in order to prove a hypothesis or answer a specific question.
- Finding a definitive answer is the central goal of any experimental process.

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Applied nutritional investigation

Vitamin D supplementation and outcomes in coronavirus disease 2019 (COVID-19) patients from the outbreak area of Lombardy, Italy

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Highlights

- Vitamin D has antiinflammatory and immunoregulatory functions.
- The involvement of vitamin D in the pathophysiology of coronavirus disease 2019 (COVID-19) is still not clear.
- Some studies support a link between vitamin D deficiency and worse COVID-19 outcomes.
- Vitamin D may also enhance macrophage activation and aberrant immune response.
- In our study, vitamin D supplementation was associated with a trend toward higher mortality.
- Supplementation trials are crucial to clarify the role of vitamin D in COVID-19.

Introduction

Recent literature has substantially raised interest in the immune-modulating properties of vitamin D against coronavirus disease 2019 (COVID-19). Although several viewpoints have been published, data supporting the hypothesized beneficial role are limited and controversial [1,2]. Consistent with a systematic review reporting the protective role of 25-hydroxyvitamin D (25OHD) supplementation [3], in a recent survey conducted in individuals with Parkinson disease (PD), those with COVID-19 were more likely not to be taking supplements than participants who were unaffected [4]. The observation of lower mortality rates at lower degrees of latitude, along with other preliminary reports on the association between serum levels of 25OHD and the risk of having the disease or a critical outcome, have suggested that vitamin D could modulate the risk and mitigate the severity of COVID-

Methods

The study was approved by local institutional ethics committees, and written informed consent was obtained from every participant.

Two sets of data collected prospectively during the outbreak of the pandemic in the north of Italy were pooled and analyzed. The first consisted of COVID-19 PD patients (group 1) and COVID-19 PD caregivers (group 2) identified from a pool of

Results

Overall, 324 COVID-19 cases were included: 105 in group 1 (PD patients), 92 in group 2 (PD caregivers), and 127 in group 3 (hospital inpatients). The characteristics of the study participants are summarized in Table 1. The use of 25OHD supplements (mean intake, 58.846 IU/mo) was reported by 38 (11.7%) participants out of 324. Clinical and demographic features of supplement users and non-users were comparable. Serum 25OHD levels of supplemented inpatients (n = 11) were about 3-fold higher than those of non-users. However, among these participants, two had insufficient levels (20—30 ng/mL; range, 24.7—29.4 ng/mL) and three presented a deficiency status (<20 ng/mL; range, 18.0—19.7 ng/mL). Forty-three (21.8%) out of 197 participants with COVID-19 identified through the phone survey required hospitalization, and 47 (27.6%) of hospitalized patients (n = 170) died. The use of 25OHD supplements was not associated with either hospitalization or in-hospital mortality, although a trend toward a 2-fold higher risk of death was found for supplement users, particularly after adjusting

Discussion

In our study, 25OHD supplementation was not associated with the severity of COVID-19. On the other hand, a trend toward a 2-fold higher mortality in users was found.

ipants assessed.

In conclusion, 25OHD supplementation was not associated with hospitalization but appeared to be a risk factor for higher in-hospital mortality in COVID-19. Further studies are needed to clarify the role of vitamin D supplementation and status in modulating the severity of COVID-19, as well as preventing it.

References

[1] Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS-CoV-2 infection? Med Drug Discov 2020;6:100041.

[2] Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J Infect Public Health 2020;13:1373–80.

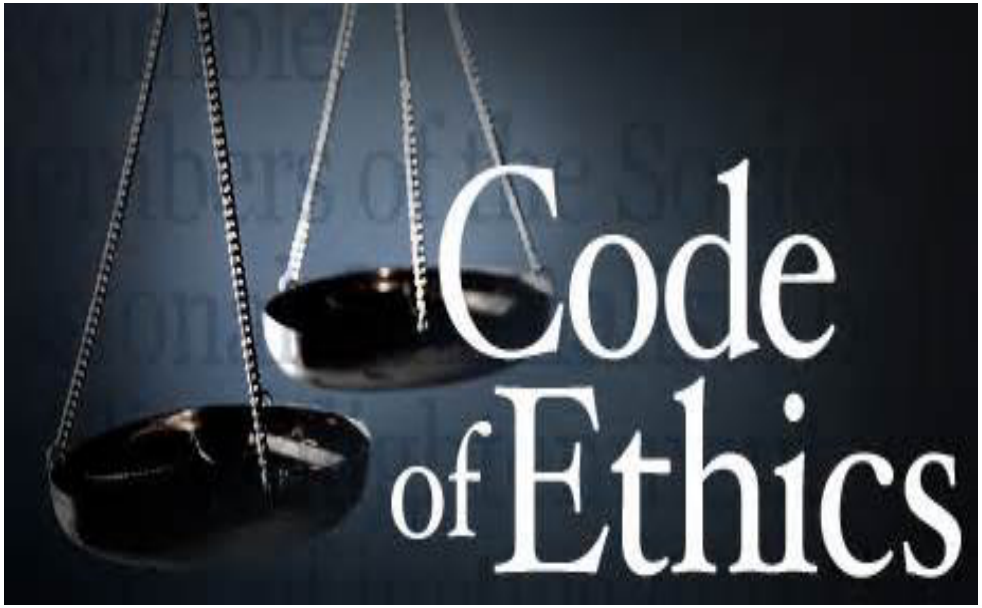
[3] Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 2017;356:i6583.

[4] Fasano A, Cereda E, Barichella M, Cassani E, Ferri V, Zecchinelli AL, et al. COVID-19 in Parkinson's disease patients Living in Lombardy, Italy. Mov Disord 2020;35:1089–93.

When scientists started get attention about ethics?:

- **It started after the abuse of human lives during Holocaust.**
- **Nuremberg Code is a set of research ethics principles for human experimentation set as a result of the subsequent Nuremberg trials at the end of the Second World War..**
- **Declaration of Helsinki (1964).**

HISTORICAL EVENTS AND DEVELOPMENT OF CODE OF ETHICS



1. NAZI MEDICAL EXPERIMENTS (1933-1945)

- Unethical activities included sterilisation (castration), mutilating surgeries and numerous medical experiments in Nazi concentration camps against prisoners in war.

- “Sterilised Jews whom Nazis considered as racial enemies”

-

(Horrific experiments were carried out in concentration camps

by fascist doctors in Germany and Japan during the 1939-45 war)

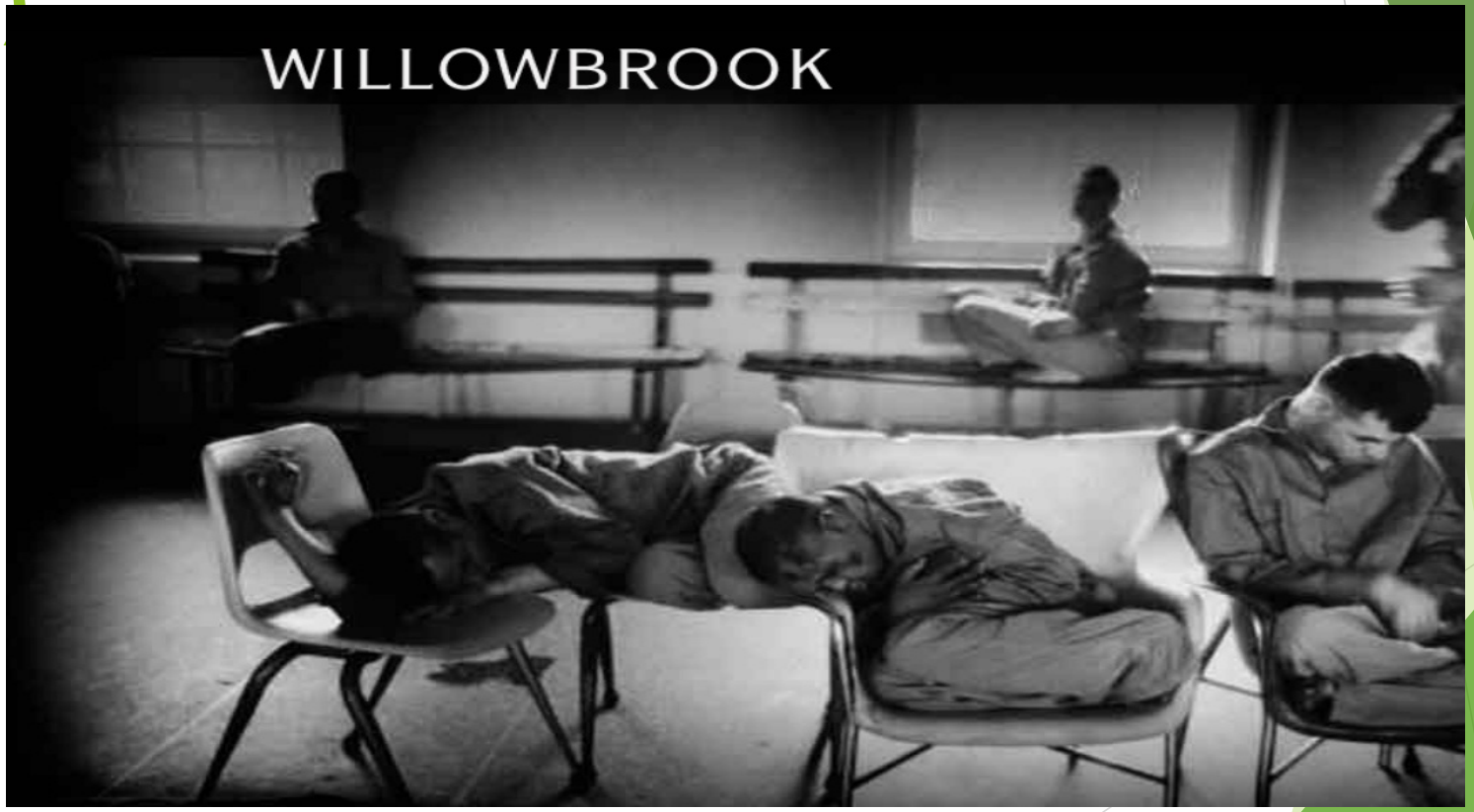
- ***Medical experiments involved exposing to high altitudes, freezing temperature, malaria, poisons, typhus fever, untested drugs and surgery without anaesthesia***
- ***Selection of subjects was racially based***
- ***Subjects had no opportunity to refuse the participation.***

- **Mistreatment of human subjects in Nazi experiments led to the development of Nuremberg Code (1947)**

International code of ethics NUREMBERG CODE-1947

- **Nuremberg Code contains 10 guidelines**
- **Voluntary consent**
- **Withdrawal of subjects from study is possible**
- **Protection of subjects from physical and mental suffering, injury, disability, and death.**
- **The balance of benefits and risks in the study.**
- The experiment should be conducted only by scientifically qualified persons
- The experiment should be so designed and based on the results of animal experimentation
- During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.
- The experiment should be such as to yield fruitful results for the good of society.

2. WILLOW-BROOK STUDY (1950-1970)

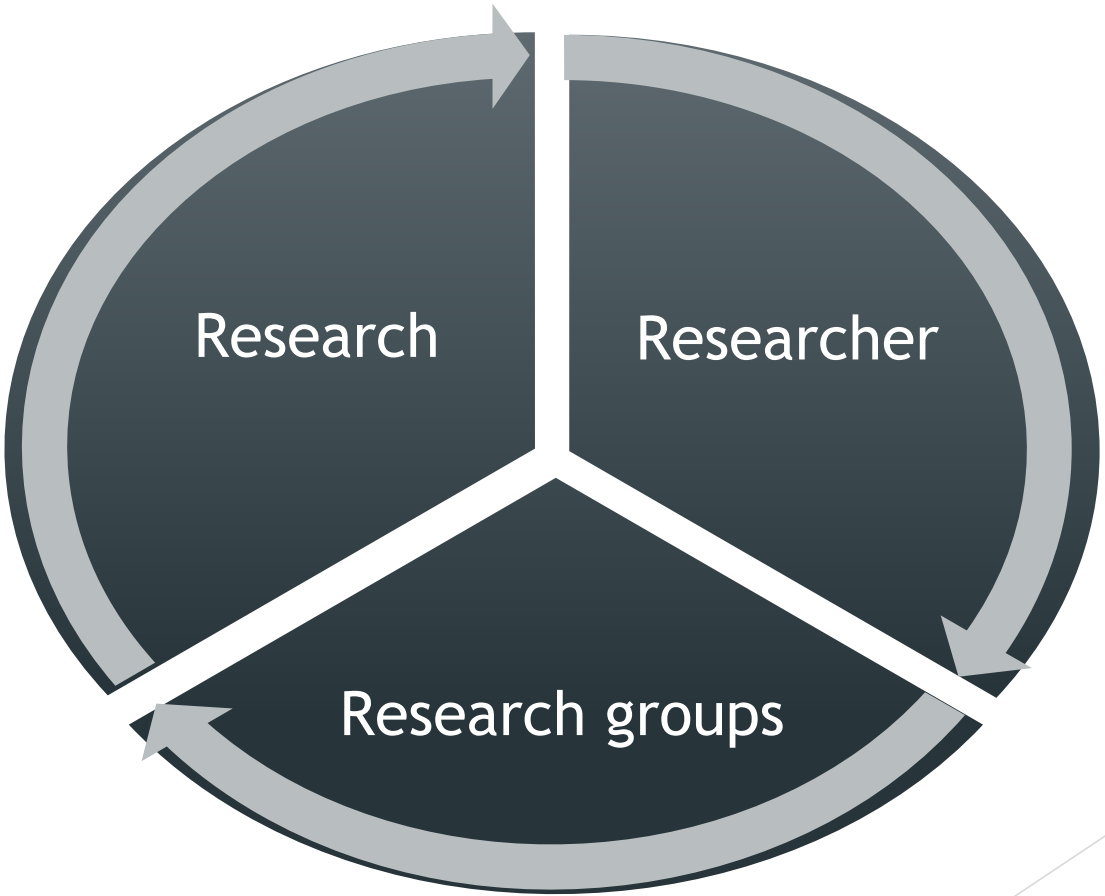


- **Research on hepatitis by Dr. Krugman at Willowbrook among mentally retarded children**
- **The researcher also wanted to determine the effectiveness of gamma globulin injections as protection against hepatitis.**
- **Early subjects were fed extracts of stool from infected individuals**
- **Later subjects received injections of purified virus**
- **Parents were forced to give permission for the child to be a subject.**

DECLARATION OF HELSINKI (1964)

- Greater care can be exercised to protect subjects from harm
- Strong, independent justification for exposing a healthy volunteer to substantial risk of harm
- Investigators must protect life and health of research subjects

Items of research




Ethics concerned the research:
Researcher
Research
Target group

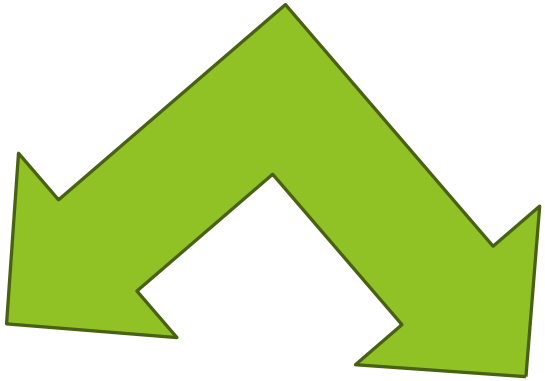
Ethics concerned the research itself:

- Follow scientific guidelines in the research.
- The research provides better alternative for the approved and used one.
- Follow the instructions as regard the environment.
- Don not violate religious rules.

The researcher should be:

- Well qualified and highly specialized.
- Collect all available data regarding the point of research.
- Follow scientific stages of the research.
- Respect research groups.
- Do not plagiarize the work of other research.

The research group: it is divided into



Animals

Human

subgroups
children
pregnant
prisoners

Animals:

- Select the suitable number (not more not less to give significant statistical results).
- Suitable species.
- Do not perform more than one experiment on the same animal.
- Use the least harmful maneuver with animals.
- Use suitable food and care for the animals.
- If the experiment involves killing the animal, use non-painful technique.

Human

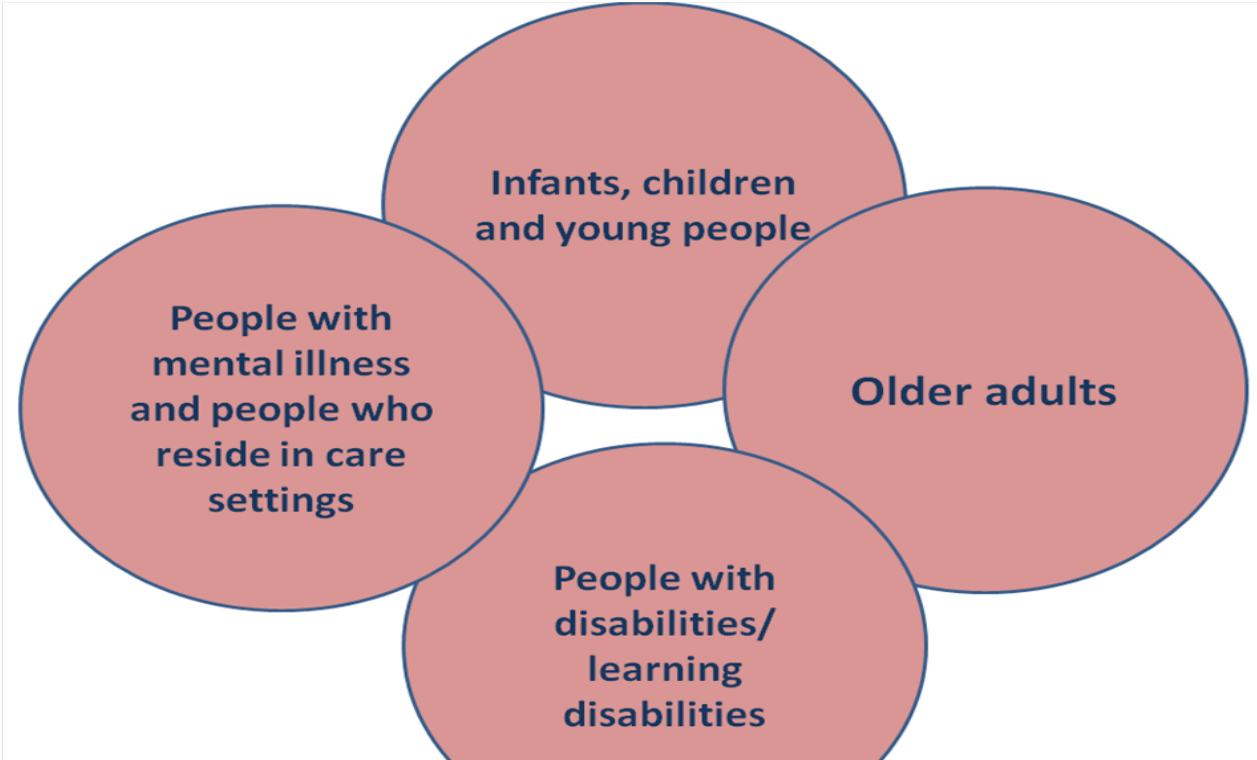
- Perform the experiment on animals before start to be tested on human.
- Obtain written **consent**:
  - Written in clear, simple language and must be explained to the volunteer by the research.
  - Contains research title, aim, procedures or steps, any side effects, and benefits of the research.
- All the volunteer to withdraw from the research at any time without threats or punish.

- Evaluation of the balance between the benefits and risk factors of the research.
- Suitable numbers of volunteers.
- Keep patients and volunteer’s data secret.
- Do best to minimize side effects and risk factors.
- Respect social and religious aspects of volunteers.
- Determine the point in which the research must stop.
- The main object of the volunteer is not gaining money.
- If any harm will occur he/she will be compensated

Research on human :

- **Experimental study:** For example, in a clinical trial of a new vaccine, the investigator may randomly assign some of the participants to receive the new vaccine, while others receive a placebo shot. The investigator then tracks all participants, observes who gets the disease that the new vaccine is intended to prevent, and compares the two groups (new vaccine vs. placebo) to see whether the vaccine group has a lower rate of disease.
- **Observational study**: the epidemiologist simply observes the exposure and disease status of each study participant. Example: cohort studies
  - **Prospective study:** Informed consent will be taken from patients. In case of incompetent patients the informed consent will be taken from the guardians.
  - **Retrospective study:** Confidentiality of records will be considered
- DNA / genomic material: Informed consent for DNA / genomic test and for research will be taken from patients. No further tests will be carried out except with further approval of committee and patients. If the samples will travel outside country the researcher will be responsible for transportation and security approval.
- All drugs used in the research are approved by the Ministry of Health

VULNERABLE SUBJECTS: sub-segment of the general public requiring maximum care and particular special protections in research. Vulnerable population require close and careful attention during the clinical trial design with notable recruitment considerations and high quality observation methods of overall safety and efficacy strategies ensuing research



Children:

- In addition to the roles that followed in adult ones; the following should be done:
  - If the research is not applicable on adult.
  - This age group should gain the benefits of the results of the research.
  - Consent is obtained from the guardians.

Pregnant and lactating women:

- Consent is obtained from wife and husband.
- Inability to perform the experiment in non-pregnant women.
- Benefits of the research focus on this group.
- No risk to the infant and children.

Prisoners:

- Prisoners must obtain full medical care.
- Consent.
- Do not use any collected data against the prisoners.
- Have the full rights as free person

When to stop the research

- It is impossible to reach the main aim of the research.
- Endanger the life of the participants.
- The risk of the research is much more than its benefits.

Ethics of stem cell research

- Source: embryo or adult
- Consent of mother for cord blood should be taken
- Consent from couple in spare embryo should be taken
- Should be used in treatment only not for cloning

II. RESEARCH MISCONDUCT

Unethical publication

- FABRICATION
- FALSIFICATION
- PLAGIARISM

Research misconduct

- *Fabrication is making up data or results and recording or reporting them.*
- *Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or* results.
- *Plagiarism is the use of another person's ideas, processes, results, or words without giving* appropriate credit and presenting them as your own.

PLAGIARISM CHECKER: soft wares

RESEARCH MISCONDUCT

- Was any type of enforcement or unnecessary influence used to recruit participants?
- Were the participants deceived in any way?
- Were appropriate informed consent procedures used?
- Were adequate steps taken to safeguard participant's privacy?

THERAPEUTIC MISCONCEPTION

- Research subject misinterpret and enrol in the study thinking it to be routine medical care

- Were vulnerable groups involved in research?

- Were groups omitted from the inquiry without a justifiable rationale?

Areas of Academic misconduct

1. Plagiarism
2. Fabrication and falsification
3. Non-publication of data
4. Faulty data-gathering procedures
5. Poor data storage and retention
6. Misleading authorship

Non-Publication of data

- Data not included in results because they don’t support the desired outcome

Authorship…

Misleading authorship—who should be an author?

- Technicians do not necessarily become joint authors.
- Authorship should involve only those who contribute directly.
- Discuss authorship before the project!

- Publication of the thesis
  - Should be regarded as the student's work
  - Students should be listed as primary authors
- Dual publication – a manuscript should only be published in a single journal
- Proper and complete referencing is an essential part of any physics research publication.
- Deliberate omission of an author or reference is unethical and unacceptable.

Research Implications

- protocol
- undertaking study
- interpretation
- making recommendations
- presenting your findings

Ethics of clinical trial & drug development

1. experimentation on animals at first (preclinical study).
2. Follow 4 phases:

- Phase I:Healthy volunteers (10-80)
- Phase II: Diseased (100-300)
- Phase III: Diseased (1000-3000)
- Phase IV: After license and marketing

Ethics of discarded tissue

- Discarded data, documents, records and specimens. (collected for purpose of diagnosis or treatment).
- all collections to have detailed records.
- all collections would have their own ethics committees.
- Informed consent should be taken.


Thank You!